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JULY 1975

The American Journal of CARDIOLOGY®

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Echocardiography in Cardiac Diagnosis

Review of Clinical Vectorcardiography

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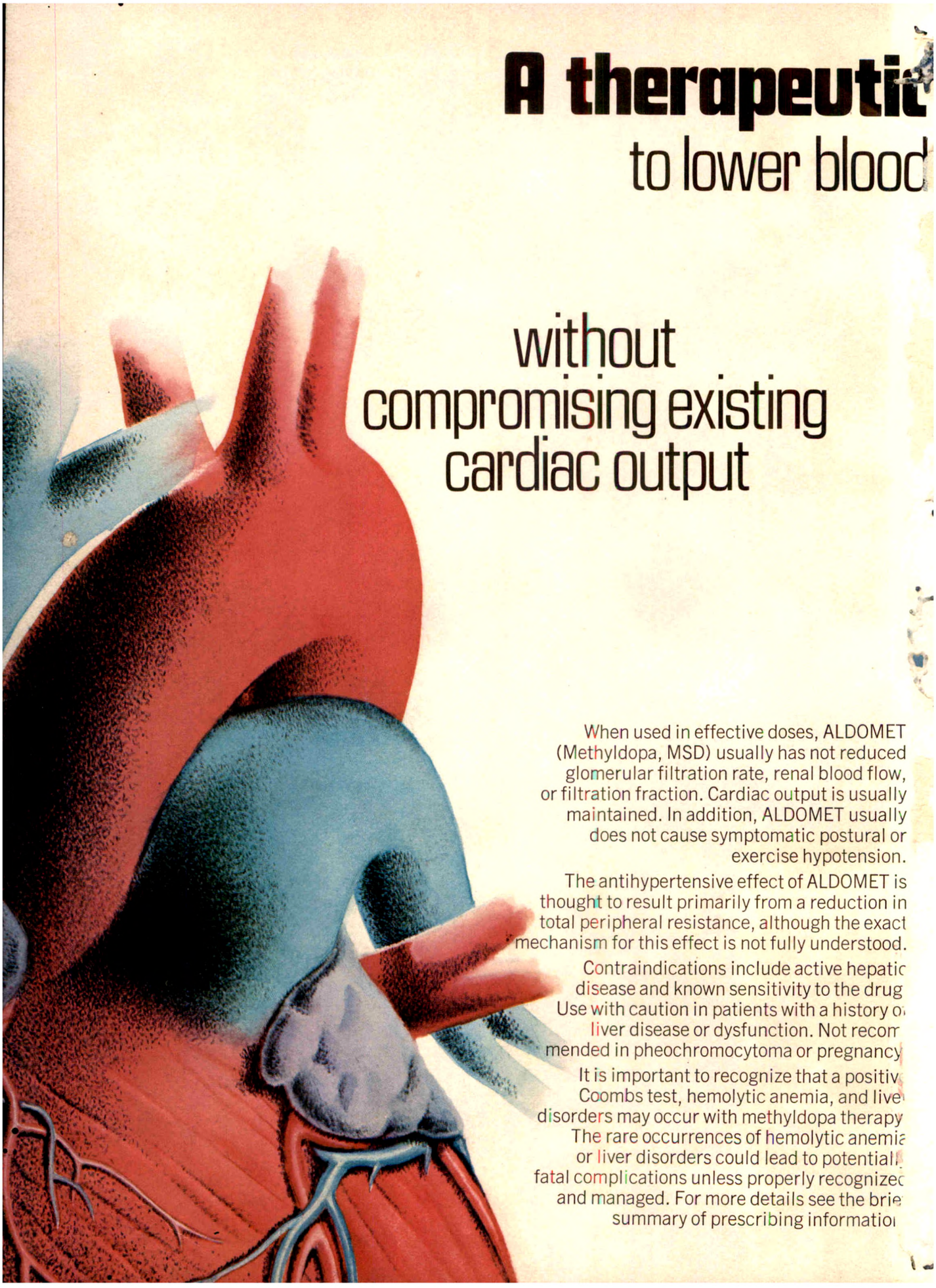

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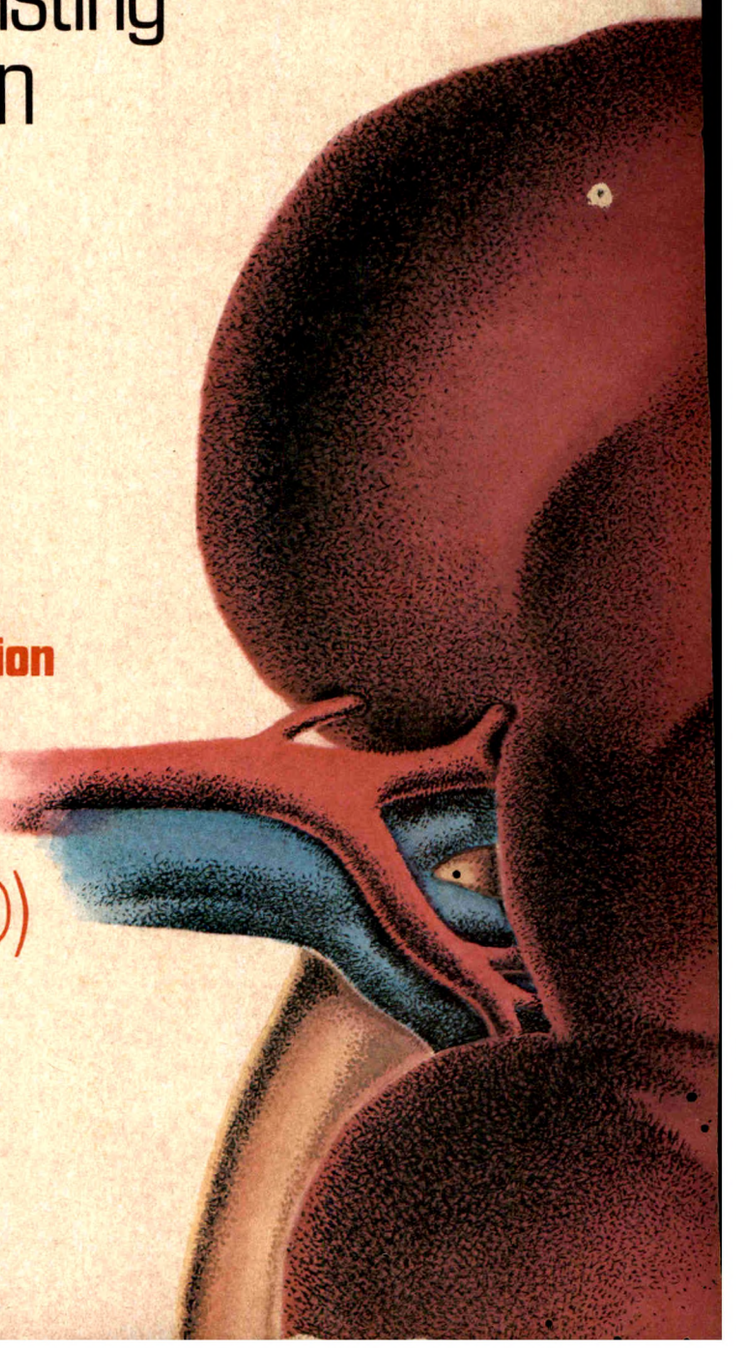

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Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis. Known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between six and twelve months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at six and twelve months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first six to twelve weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur.

Use in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Methyldopa may interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has occurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure are occasionally seen and include dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency. Angina pectoris may be aggravated. Symptoms of orthostatic hypotension may occur; if symptoms occur, reduction of dosage is suggested. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distention, constipation, flatus, and diarrhea occur occasionally; these generally can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently and are relieved by administering a thiazide diuretic; if edema progresses or signs of pulmonary congestion appear, discontinue drug. A rise in BUN has been observed. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, Bell's palsy, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Note: Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Maximal recommended daily dose is 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

How Supplied: Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

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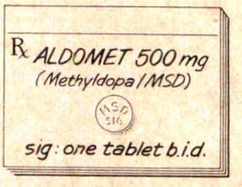

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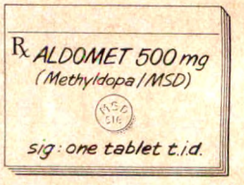

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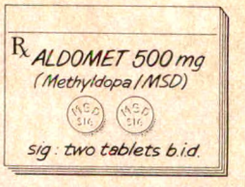

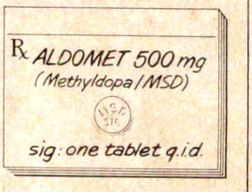

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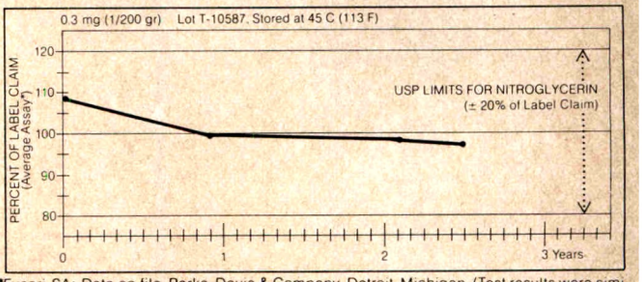

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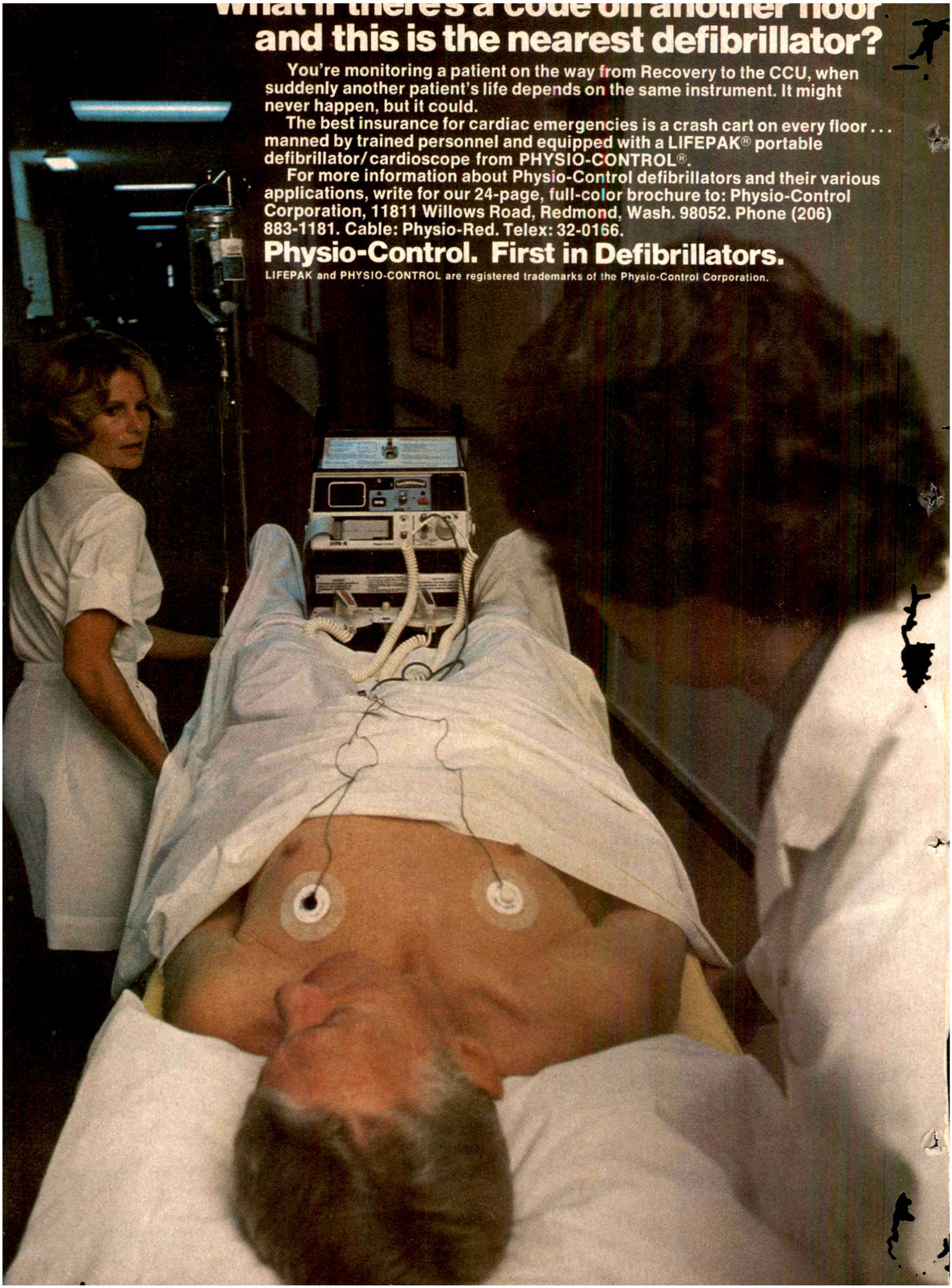
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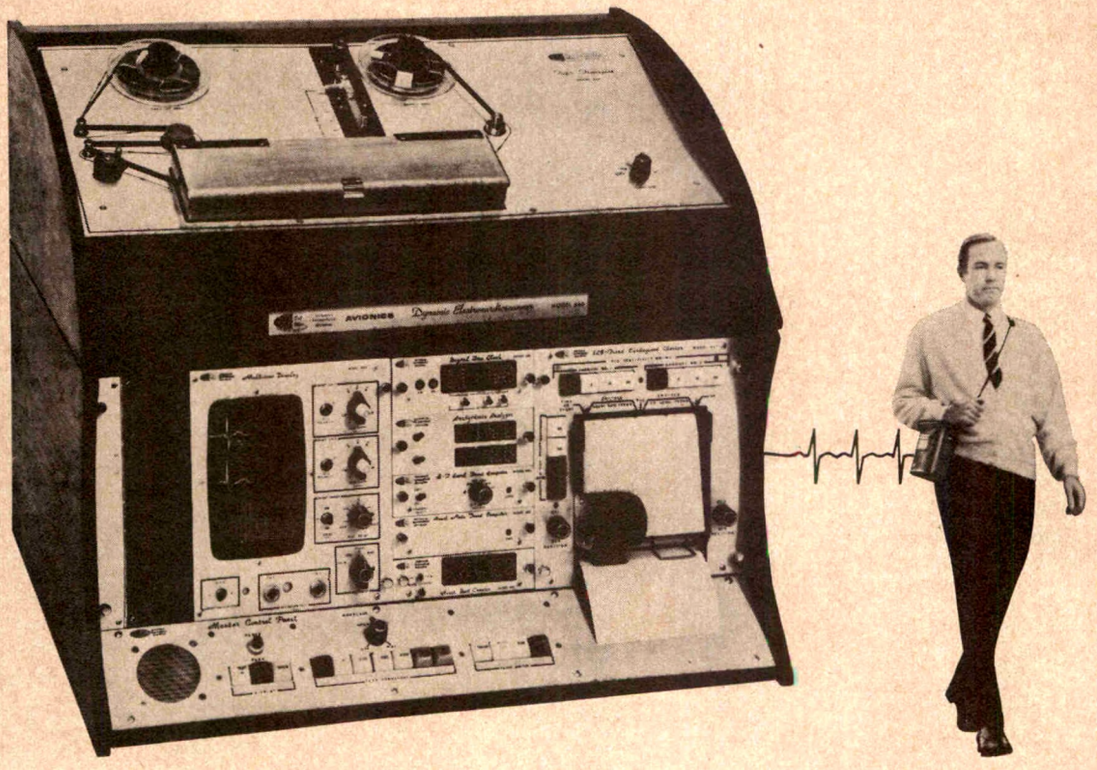

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CLINICAL STUDIES

1 **Echocardiography in Acute Myocardial Infarction**

BETTY C. CORYA, SUSAN RASMUSSEN, SUZANNE B. KNOEBEL and HARVEY FEIGENBAUM with the technical assistance of MARY JO BLACK

Echocardiograms recorded in 64 patients with acute transmural myocardial infarction during their stay in the coronary care unit proved useful in detecting abnormalities of left ventricular wall motion corresponding to the electrocardiographic site of infarction and in determining prognosis. By combining the measurement of left ventricular internal dimension (correlating with heart failure) and mitral valve closure (reflecting left ventricular end-diastolic pressure), it was possible to predict hospital mortality from the echocardiograms.

11 **Echocardiography in Aortic Root Dissection and Dilatation**

RICHARD W. MOOTHART, RICHARD D. SPANGLER and S. GILBERT BLOUNT, Jr.

Echocardiography had a diagnostic accuracy equal to that of angiography and could be repeated easily and safely in six patients with aortic root dissection and in six with aortic root dilatation. Recording of a double echo from the anterior or posterior root was diagnostic of aortic root dissection. Echocardiography was helpful not only in diagnosis but also in patient management and follow-up.

17 **Echocardiographic Criteria for Aortic Root Dissection**

OWEN R. BROWN, RICHARD L. POPP and FRANK E. KLOSTER

Previously reported echocardiographic criteria of aortic root dissections—widened posterior or anterior aortic wall (or both), parallel motion of the separated margins of the aortic root walls and aortic root dilatation—were found not only in one patient with proved aortic root dissection, but also in 5 of 10 patients without clinical indication of this condition or aortic valve disease. At least two of these criteria were also recorded in the remaining five patients. The echocardiographic diagnosis of aortic root dissection is most reliable in the presence of positive clinical indications of this condition.

21 **Echocardiographic Differentiation of Infundibular from Valvular Pulmonary Stenosis**

ARTHUR E. WEYMAN, JAMES C. DILLON, HARVEY FEIGENBAUM and SONIA CHANG

Echocardiograms in three patients with infundibular pulmonary stenosis showed marked chaotic systolic fluttering of the pulmonary valve leaflet which lies in the turbulent stream of blood distal to the obstruction. This fluttering, absent in 24 normal subjects and in 16 patients with valvular pulmonary stenosis, appears unique and useful in separating infundibular from valvular pulmonary stenosis. Another observation was normal or absent presystolic opening motion of the pulmonary valve leaflet in infundibular stenosis contrasted to the increased posterior or opening motion in valvular stenosis.

Continued on page A13

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27 **Radiographic Appearance of the Thorax in Systolic Click-Late Systolic Murmur Syndrome**

CARL P. BON TEMPO, JAMES A. RONAN, Jr., ANTONIO C. de LEON, Jr. and HOMER L. TWIGG

A striking number of thoracic skeletal abnormalities observed in 39 of 64 patients with an isolated systolic click or a systolic click with a late systolic murmur suggest that these abnormalities should be considered diagnostic features of this syndrome. Scoliosis occurred in 39 percent, a "straight back" in 23 percent and pectus excavatum in 11 percent.

32 **Thoracic Skeletal Abnormalities in Idiopathic Mitral Valve Prolapse**

JOSEPH SALOMON, PRAVIN M. SHAH and ROBERT A. HEINLE

Thoracic skeletal abnormalities in 24 patients with proved prolapse of the mitral valve include pectus excavatum (62 percent), "straight back" (17 percent) and severe scoliosis (8 percent). Patients with such skeletal abnormalities should be checked carefully for mitral valve prolapse. The combination of mitral valve prolapse and these skeletal deformities may represent a forme fruste of Marfan's syndrome.

EXPERIMENTAL STUDIES

37 **Termination of Ventricular Fibrillation in Dogs by Depolarizing a Critical Amount of Myocardium**

DOUGLAS P. ZIPES, JOHN FISCHER, ROBERT M. KING, ANN deB. NICOLL and WALTER W. JOLLY

These experiments in dogs support the concept that a critical myocardial mass is required to maintain ventricular fibrillation initiated by rapid ventricular pacing. Successful defibrillation resulted when a critical amount of myocardium was depolarized by either potassium chloride or electrical discharge. Not every cell in both ventricles must be depolarized to terminate ventricular fibrillation in the entire heart.

45 **Influence of Sympathetic Tone on Ventricular Fibrillation Threshold During Experimental Coronary Occlusion**

BERNARD R. KLIKS, MARY JO BURGESS and J. A. ABILDSKOV

The ventricular fibrillation threshold in 14 open chest dogs with controlled heart rate decreased 35 percent during coronary occlusion, 42 percent during stellate stimulation and 63 percent during combined coronary occlusion and stellate stimulation. Stellectomy in seven animals increased the threshold 31 percent. After stellectomy, coronary occlusion decreased the ventricular fibrillation threshold by only 11 percent. These findings may have therapeutic implications for treatment of ventricular arrhythmias caused by myocardial infarction or central nervous system disease.

50 **Effect of Manganese Chloride and Verapamil on Automaticity of Digitalized Purkinje Fibers**

WARREN W. TSE and JAOK HAN

Manganese chloride and verapamil suppressed the ouabain-induced increase in automaticity of isolated spontaneously beating Purkinje preparations. This suggests that an inward calcium ion current may be involved in the development of digitalis-induced increase in the slope of phase 4 depolarization in Purkinje fibers.

Continued on page A15

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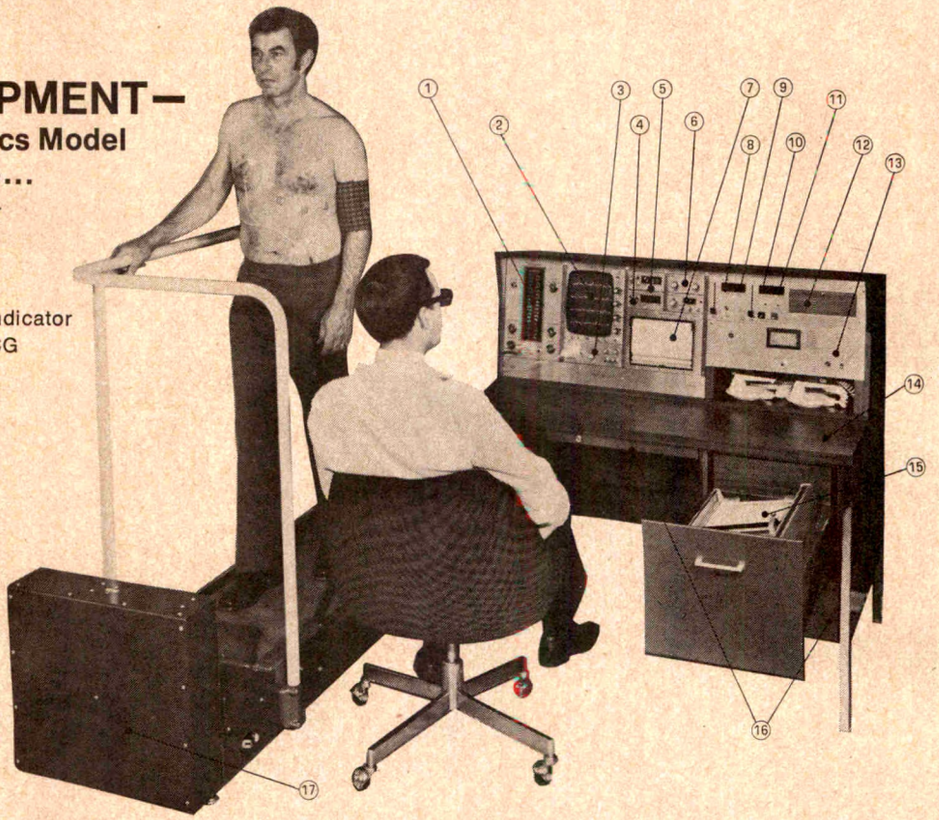

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56 Use of a Balloon-Tipped Flotation Electrode Catheter for Cardiac Monitoring

KANU CHATTERJEE, H. J. C. SWAN, WILLIAM GANZ, RICHARD GRAY, HANNAN LOEBEL, JAMES S. FORRESTER and DAVID CHONETTE

This special balloon-tipped flotation catheter with two pairs of electrodes permits simultaneous monitoring of cardiac rhythms and hemodynamics at the bedside and, when indicated, atrial, ventricular or atrioventricular sequential pacing. Major problems associated with its use are the need for several catheters with differences in distance between the electrodes and the catheter tip and between electrodes to accommodate heart chambers and great vessels of various sizes. Important benefits for diagnosis and management can be achieved in patients with hemodynamic difficulties and arrhythmias.

62 Retrograde Catheterization of the Left Atrium in Idiopathic Hypertrophic Subaortic Stenosis

BERT WONG, RENE A. LANGOU, LAWRENCE S. COHEN and STEVEN WOLFSON

Retrograde catheterization of the left atrium utilizing the Shirey technique, easily and successfully performed in four patients with idiopathic hypertrophic subaortic stenosis, is recommended as an alternative to the transseptal approach to the left atrium in this condition. By traversing the inflow tract of the left ventricle during pullback from the left atrium to the aorta, differentiation of true subaortic stenosis from cavity obliteration is facilitated.

PEDIATRIC CARDIOLOGY

67 Right Ventricular Volume in Congenital Heart Disease

ELIZABETH A. FISHER, IRA W. DuBROW and ALOIS R. HASTREITER

This investigation indicates that a simple geometric model, a prism with a triangular base, is comparable in accuracy with Simpson's rule both in cast studies and in in vivo calculations of right ventricular volume. The normal right ventricle in children is slightly larger than the left and has a lower ejection fraction. In children the right ventricle can adapt to chronic increase in afterload and preload and is not necessarily overloaded by a ventricular septal defect or tetralogy of Fallot. It is relatively unaffected by severe myocardial disease.

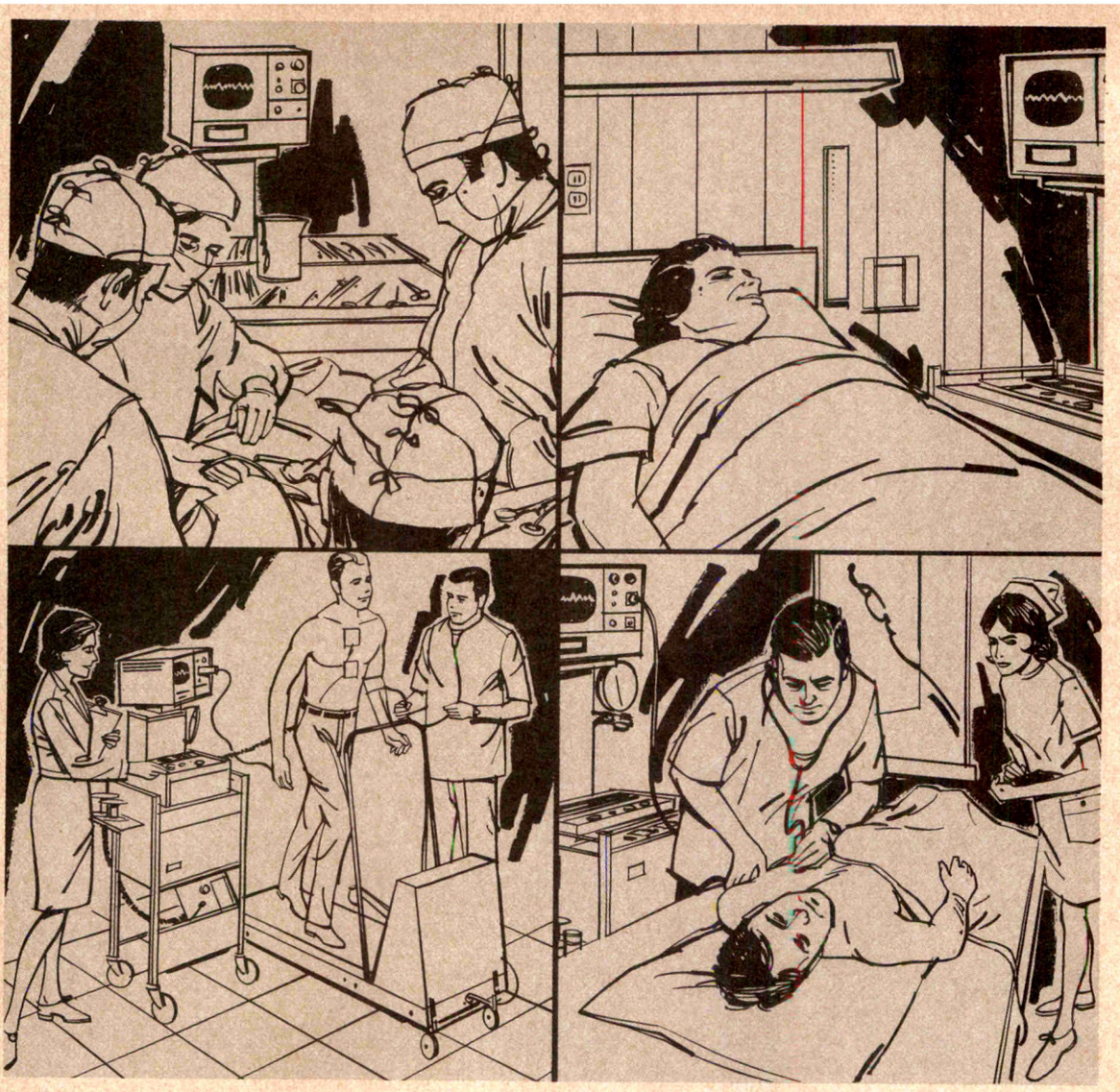
REVIEWS

76 Advances in Clinical Vectorcardiography

ALBERTO BENCHIMOL and KENNETH B. DESSER

Experience in more than 5,000 patients subjected to complete right and left heart catheterization and selective coronary cineangiography demonstrates the clinical superiority of the vectorcardiogram over the electrocardiogram in the recognition of atrial and ventricular hypertrophy, identification of myocardial infarction and the diagnosis of multiple infarctions in the presence of fascicular and bundle branch blocks. It is suggested that the Frank lead system be used in all clinical vectorcardiographic laboratories and become part of the noninvasive evaluation of patients with cardiac disease.

Continued on page A17



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MILTON J. SANDS, THOMAS H. KREULEN, MICHAEL T. McDONOUGH, MONEIM A. FADALI and JAMES F. SPANN

A significant increase in the amount of paravalvular aortic regurgitation in a 32 year old man with aortic and mitral valve prostheses prematurely closed the mitral valve in mid-diastole. Oversewing of the aortic and mitral paravalvular leaks normalized mitral prosthetic function.

91 **Limitations of the Surface Electrocardiogram in Diagnosis of Atrial Arrhythmias. Further Observations on Dissimilar Atrial Rhythms**

DELON WU, PABLO DENES, FERNANDO AMAT y LEON, RAMESH C. CHHABLANI and KENNETH M. ROSEN

Electrophysiologic studies in two patients with atrial dysrhythmias demonstrate that under unusual circumstances the surface electrocardiogram may not accurately portray atrial activation in the presence of advanced atrial disease. Multiple intracavitary electrograms may be necessary for accurate diagnosis.

CASE REPORTS

98 **"Paradoxical" Prolongation of Sinus Nodal Recovery Time After Atropine in the Sick Sinus Syndrome**

JAMES A. REIFFEL, J. THOMAS BIGGER and ELSA-GRACE V. GIARDINA

After the administration of atropine in a 55 year old woman with sick sinus syndrome, the sinus recovery time became markedly prolonged and atrial quiescence persisted more than 10 seconds, presumably because of alterations in sinus nodal automaticity, sinoatrial conduction time or intra-sinoatrial nodal conduction. These results suggest that an increase in post-tachycardia bradycardia produced by atropine could aggravate symptoms in such patients.

105 **Demand Pacemaker Arrhythmias Caused by Intermittent Incomplete Electrode Fracture. Diagnosis with Testing Magnet**

PHILIPPE COUMEL, JACQUES MUGICA and S. SERGE BAROLD

Abrupt changes in resistance within a pacing system cause corresponding voltage changes between the anode and cathode and may generate false signals that can be sensed by a demand pulse generator. Such false signals should be suspected whenever demand pacing produces a chaotic pattern. This report shows how a testing magnet was used to diagnose intermittent partial electrode fracture in two patients with an implanted demand pacemaker.

EDITORIALS

110 **Etiology of the Mitral Valve Prolapse-Click Syndrome**

ROBERT M. JERESATY

Continued on page A19

ACCEPTED CONCEPTS IN ANGINA THERAPY*

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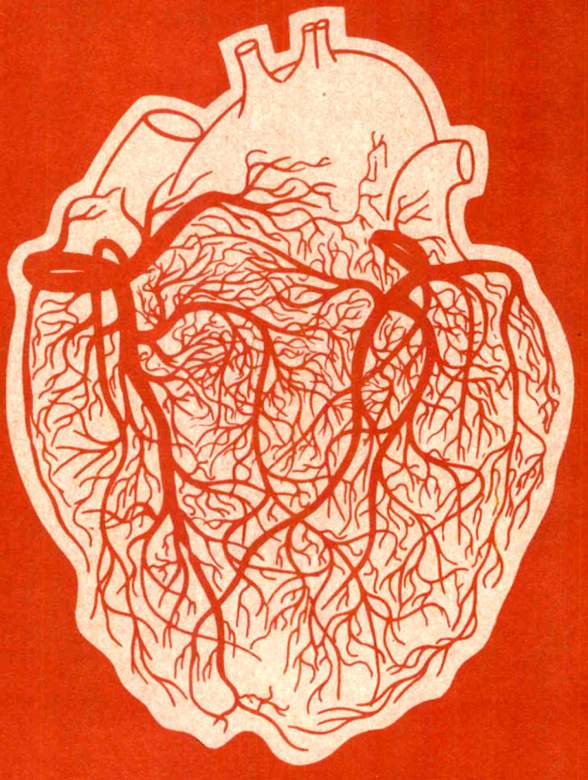

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"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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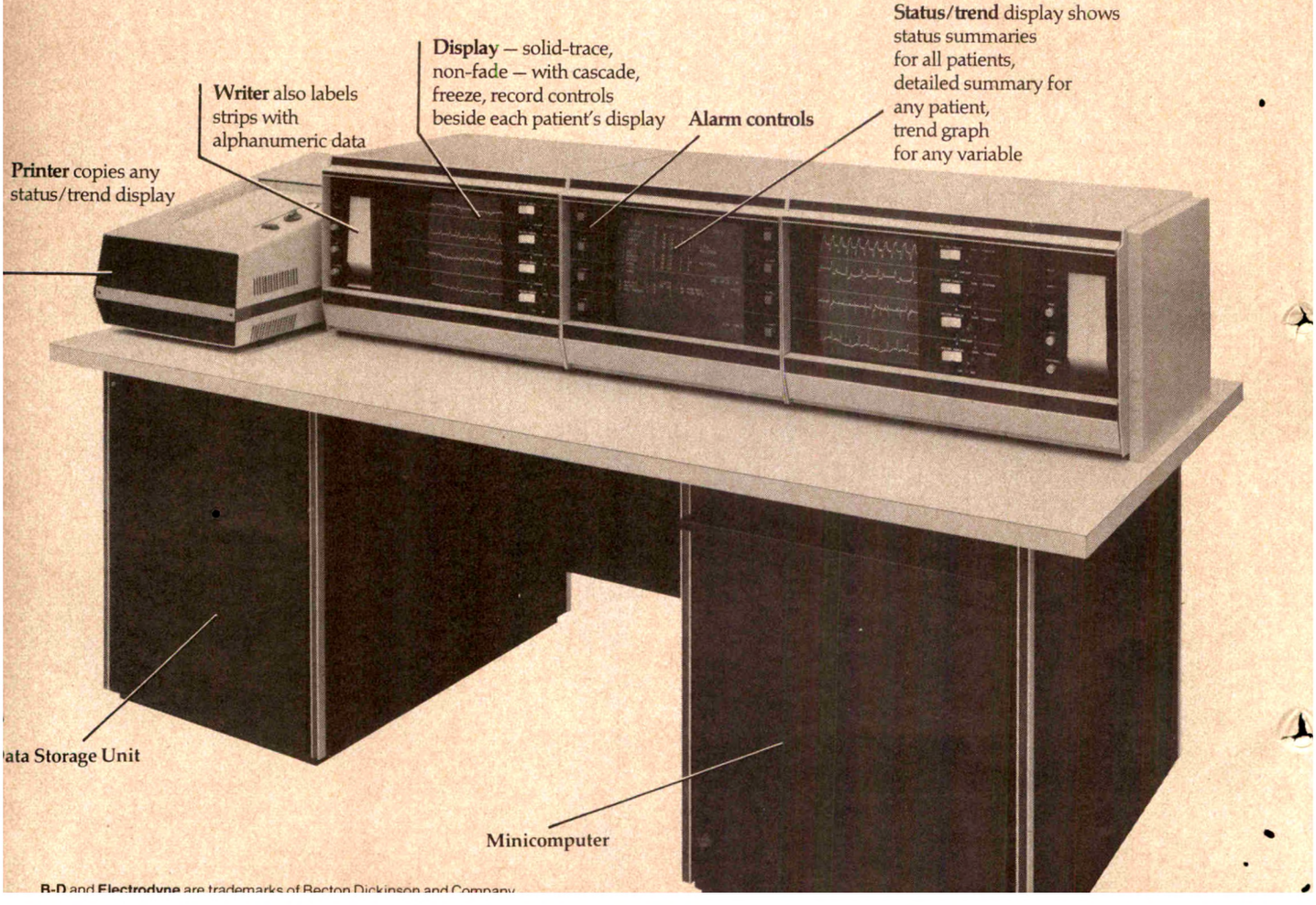

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meaning to monitoring.

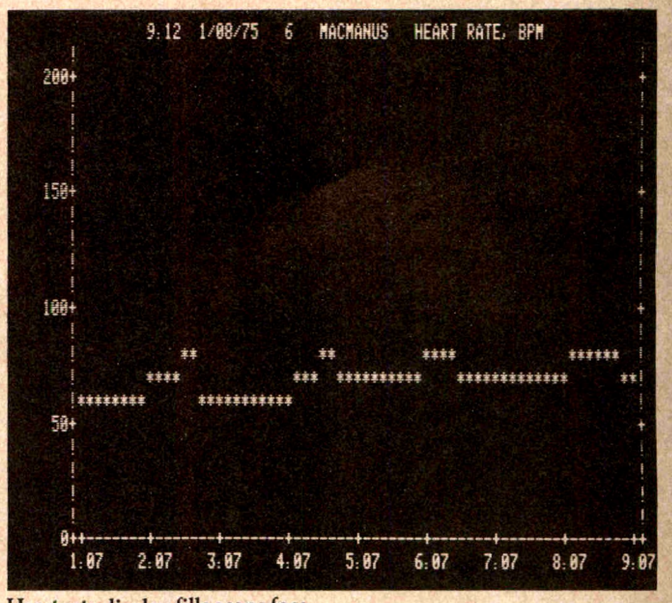
BED	NAME	HR	LIMITS	VPB	LIMIT	STATUS
1	MARCHESSEAULT	78	60 115	7	5	HIGH VPB RATE
2	HUTCHINGS	73	50 110	1	3	
3	SEABURY	53	50 120	0	5	A FIB
4	CORRIGAN	81	55 120	2	4	
5	DESLILE	138	50 120	0	5	V TACH
6	MACMANUS	67	55 115	12	20	BIGEMINY
7	RATHKAMP	74	50 120	0	5	HIGH SVPB RATE
8	SHUMAN	70	50 120	0	5	

8 SHUMAN ADM: 15:23 1/06

			LIMITS				LIMITS
#1	HEART RATE	T 70	50 120	#4	SVPB RATE	T 0	10
#2	VPB RATE	T 0	5	#5	PAIRS RATE	0	2
#3	EARLY VPB RATE	T 0	2				

9:11 1/08/75

Clearly visible status summary on central station display



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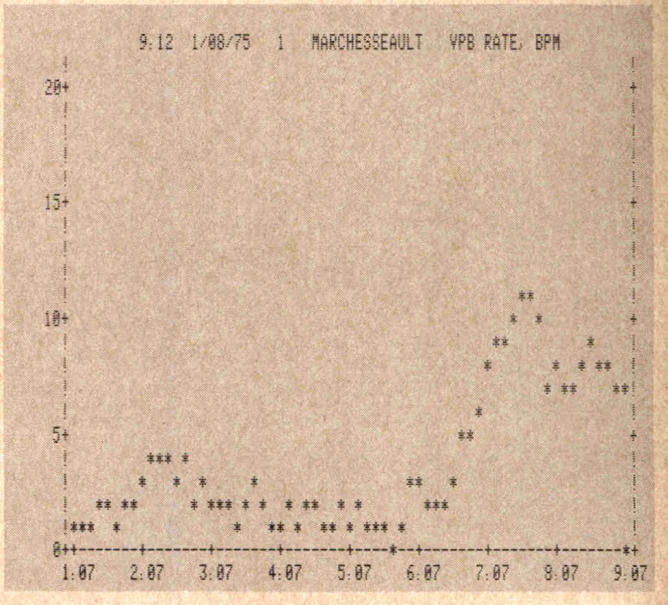

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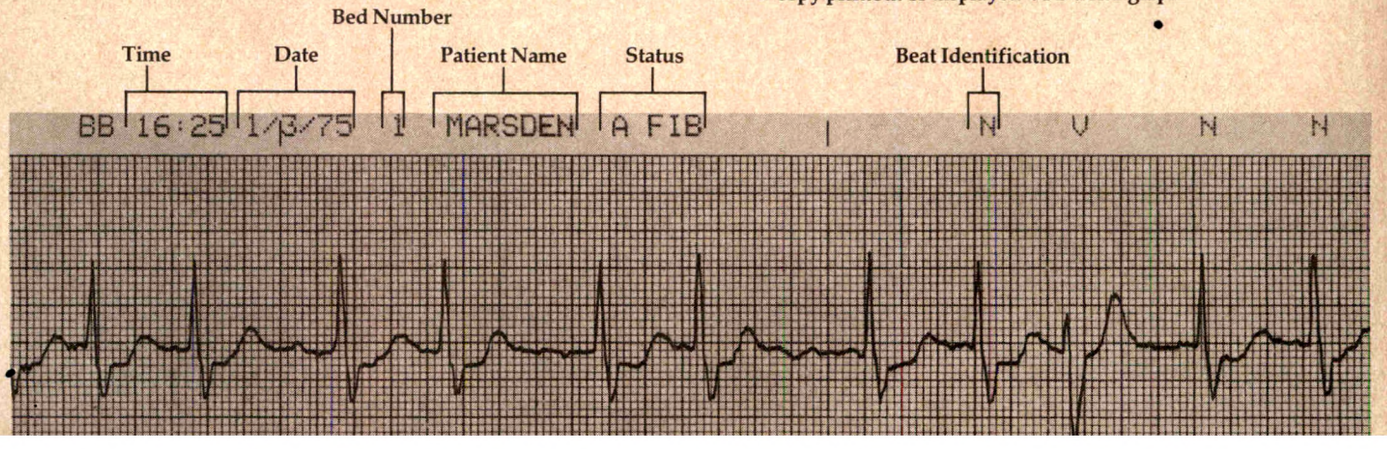

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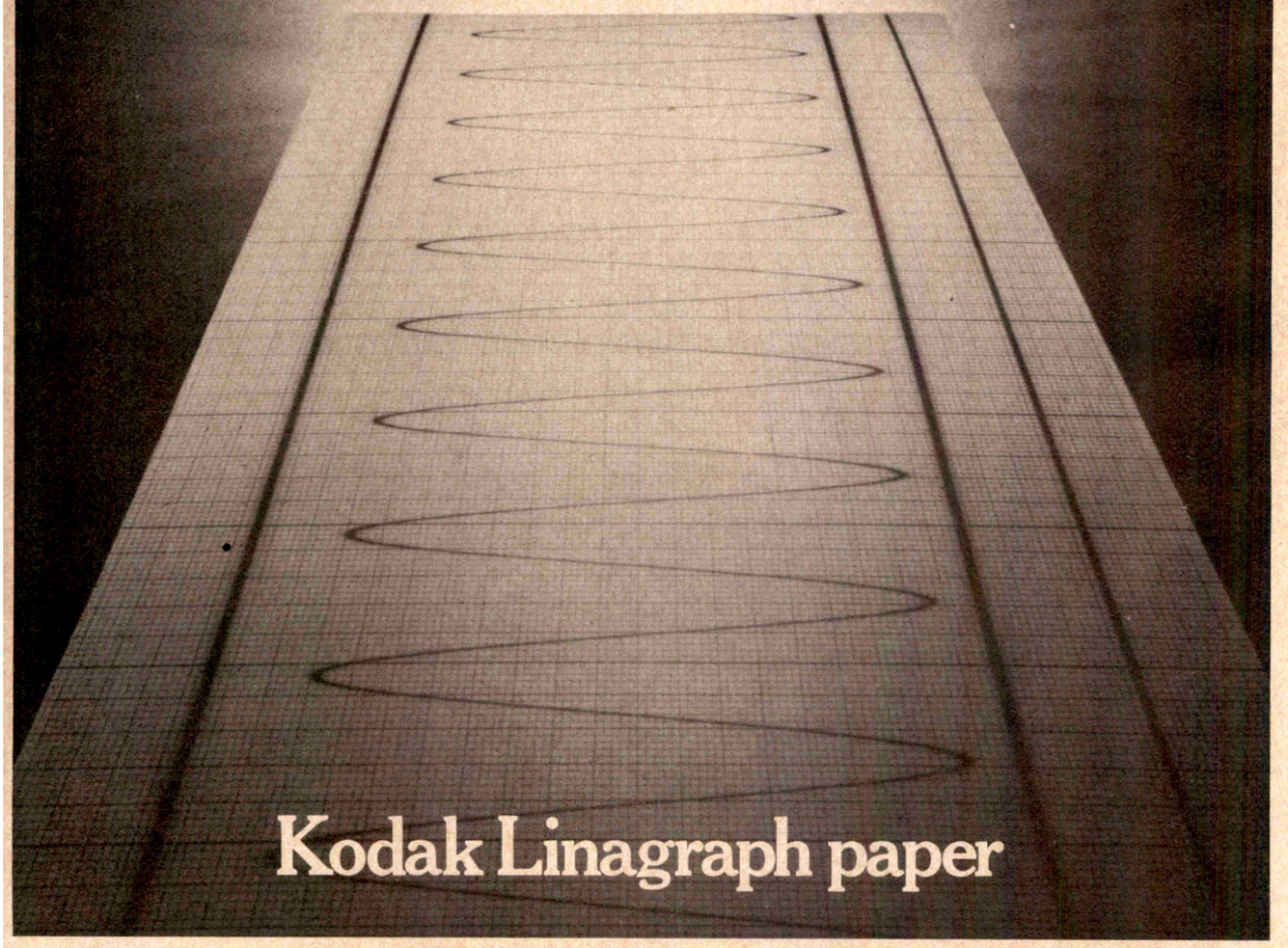

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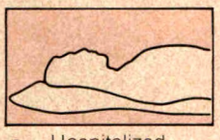
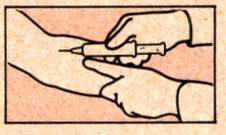
*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J* 87(6): 791-795, June 1974.

Administration guidelines



1. Hospitalized patient should be recumbent.

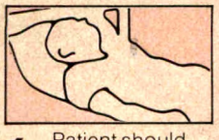
2. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml. ampule contains 300 mg. diazoxide).



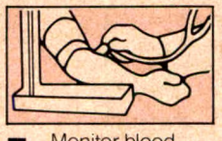
3. Insert needle only into a peripheral vein.

4. Inject entire dose I.V. in 30 seconds or less.

5. Remove needle carefully—avoid extravasation.

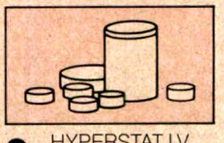


6. Patient should remain recumbent for at least half an hour after injection.



7. Monitor blood pressure closely until stabilized—usually 15-30 minutes.

8. If patient is to be ambulatory, blood pressure should be measured in standing position before surveillance is ended.



9. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective—generally within a few days.

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Actions HYPERSTAT I.V. Injection produces a prompt reduction in blood pressure by relaxing smooth muscle in the peripheral arterioles. Cardiac output is increased as blood pressure is reduced by diazoxide; coronary and cerebral blood flow are maintained. Renal blood flow is increased after an initial decrease. Diazoxide has no known direct action on the central nervous system.

Patients refractory to other antihypertensive agents usually remain responsive to diazoxide.

Diazoxide is extensively bound to serum protein (>90%). The plasma half-life is 28 ±8.3 hours; however, the duration of its antihypertensive effect is variable, generally lasting less than 12 hours. Although an antihypertensive response has been obtained with slow intravenous injection, in general, a greater antihypertensive effect is obtained with rapid intravenous administration.

Indications HYPERSTAT I.V. Injection is indicated for the emergency reduction of blood pressure in malignant hypertension in hospitalized patients, when prompt and urgent decrease of diastolic pressure is required. Treatment with orally effective antihypertensive agents should be instituted as soon as the hypertensive emergency is controlled.

HYPERSTAT (diazoxide) I.V. Injection is ineffective against hypertension due to pheochromocytoma.

Contraindications HYPERSTAT I.V. Injection should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt.

The drug should not be used in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

Warnings **Usage in Pregnancy:** The safety of HYPERSTAT I.V. Injection in pregnancy has not yet been established.

Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults.

Usage in Children: The safety of HYPERSTAT I.V. Injection in children has not yet been established.

Hypotension may occasionally result from the administration of HYPERSTAT I.V. If hypotension severe enough to require therapy occurs, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine.

Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide.

Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. It should be noted that concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions).

Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent.

Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

Precautions HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available when HYPERSTAT I.V. Injection is used.

HYPERSTAT I.V. Injection should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively.

Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response.

As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental.

Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection.

Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

Adverse Reactions

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial and/or cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; unconsciousness, convulsions, paralysis, or confusion; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported.

Other adverse reactions: Nausea, vomiting, and/or abdominal discomfort; vasodilative phenomena, such as flushing, generalized or localized sensations of warmth, headache (sometimes throbbing), and sweating; orthostatic hypotension, lightheadedness, and weakness of short duration; supraventricular tachycardia and palpitation; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; nonanginal "tightness in the chest"; warmth or pain along the injected vein; cellulitis without sloughing and/or phlebitis at the site of extravasation; anorexia and alteration of taste; ileus; bradycardia; back pain; chest discomfort; dyspnea, choking sensation; apprehension or anxiety, malaise, and blurred vision occurred on single occasions; parotid swelling, salivation, lacrimation; ringing in the ears; diarrhea and constipation; increased nocturia; euphoria.

Drug Interactions Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

Overdosage Overdosage of HYPERSTAT I.V. Injection may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy of hyperglycemia.

Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

Animal Pharmacology and Toxicology In studies involving a number of species, including the rat, cat, dog, and monkey, diazoxide has been shown to exert significant antihypertensive actions through its direct effect on peripheral arterioles, which neither impairs cardiac function nor seriously diminishes perfusion of kidneys. In addition, in each species tested, including the rat, dog, and monkey, diazoxide elicits hyperglycemia, increased serum-free fatty acids and decreased plasma insulin levels by a mechanism thought to involve both suppression of insulin release and enhanced catecholamine action.

Although the data are not conclusive, reproduction and teratology studies in several species of animals indicate that diazoxide, when administered during the critical period of embryo formation, may interfere with normal fetal development, possibly through altered glucose metabolism. Parturition was occasionally prolonged in animals treated at term.

Dosage and Administration HYPERSTAT I.V. Injection is administered undiluted and rapidly by intravenous injection. It should only be given into a peripheral vein. Do not administer it intramuscularly, subcutaneously, or into body cavities. Avoid extravasation of the drug into subcutaneous tissues.

The response to HYPERSTAT I.V. Injection varies from patient to patient. Generally, blood pressure decreases within five minutes, often within one to two minutes, to the lowest level achieved. The blood pressure increases relatively rapidly in the next ten to 30 minutes, and then more slowly over the following two to 12 hours, nearly reaching but rarely exceeding the pretreatment level. The response to successive injections is frequently better than that to the initial injection.

Treatment of hypertensive emergencies with HYPERSTAT I.V. Injection should be limited to a few days and a regimen of oral antihypertensive medications should be instituted as soon as possible.

With the patient recumbent, the contents of one 20 ml. ampule containing 300 mg. of HYPERSTAT I.V. Injection are administered intravenously in 30 seconds or less. Slow intravenous injection may fail to reduce the blood pressure or may produce an exceedingly short response.

Specific dosage is required in children or in unusually large or small patients. This dosage may be calculated on the basis of 5 mg./kg. body weight (0.3 ml./kg.) (See Warnings).

A second administration of HYPERSTAT (diazoxide) I.V. Injection may be required for a satisfactory reduction in blood pressure, if the first injection fails to give an adequate response within 30 minutes.

Repeated administration of HYPERSTAT I.V. Injection at intervals of four to 24 hours usually will maintain the blood pressure below pretreatment levels until a regimen of oral antihypertensive medication becomes effective. The interval between injections may be adjusted by the duration of the response to each injection. It is usually unnecessary to continue treatment with HYPERSTAT I.V. Injection for more than four to five days.

Following the use of HYPERSTAT I.V. Injection, the blood pressure should be monitored closely until it has stabilized. Thereafter, measurements taken hourly during the balance of the effect will indicate any unusual response. A further decrease in blood pressure at 30 minutes or more after injection should be investigated for causes other than the action of HYPERSTAT I.V. Injection. It is preferable that the patient remain recumbent for half an hour after injection. In ambulatory patients, the blood pressure should be measured with the patient standing before surveillance is ended.

Since repeated administration of HYPERSTAT I.V. Injection can lead to sodium and water retention, administration of a diuretic may be necessary both for maximal blood pressure reduction and to avoid congestive failure.

How Supplied HYPERSTAT I.V. Injection is supplied in a 20 ml. ampule containing diazoxide 300 mg. in a clear, colorless aqueous solution; box of one ampule.

Protect from light and freezing.

Store away from heat.

AUGUST 1973

20 ml.
in 30 seconds or less
for direct action.

SWW-4940

Schering

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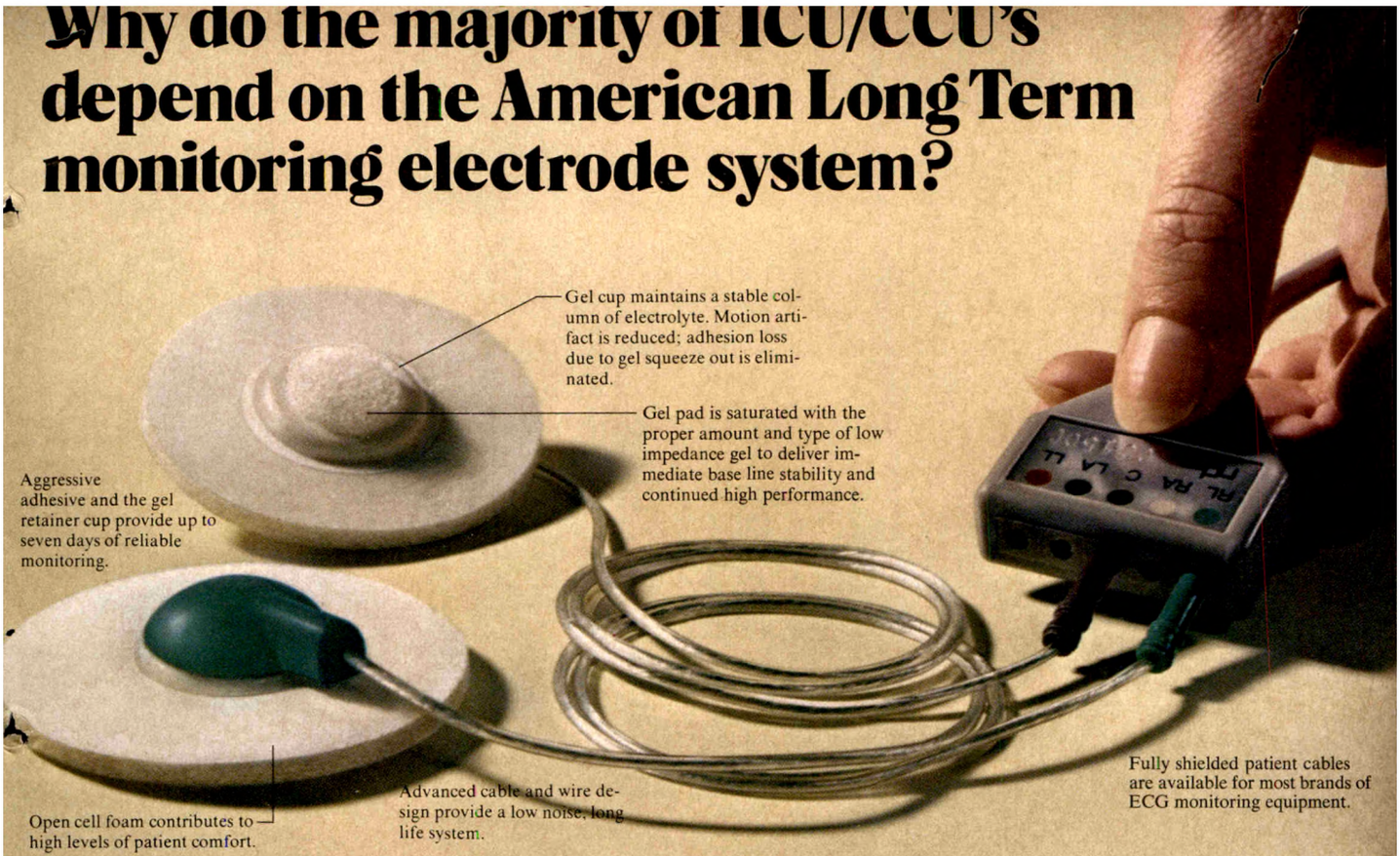
Why do the majority of ICU/CCU's depend on the American Long Term monitoring electrode system?



This is the system that has established new standards for high performance in long term ECG monitoring.

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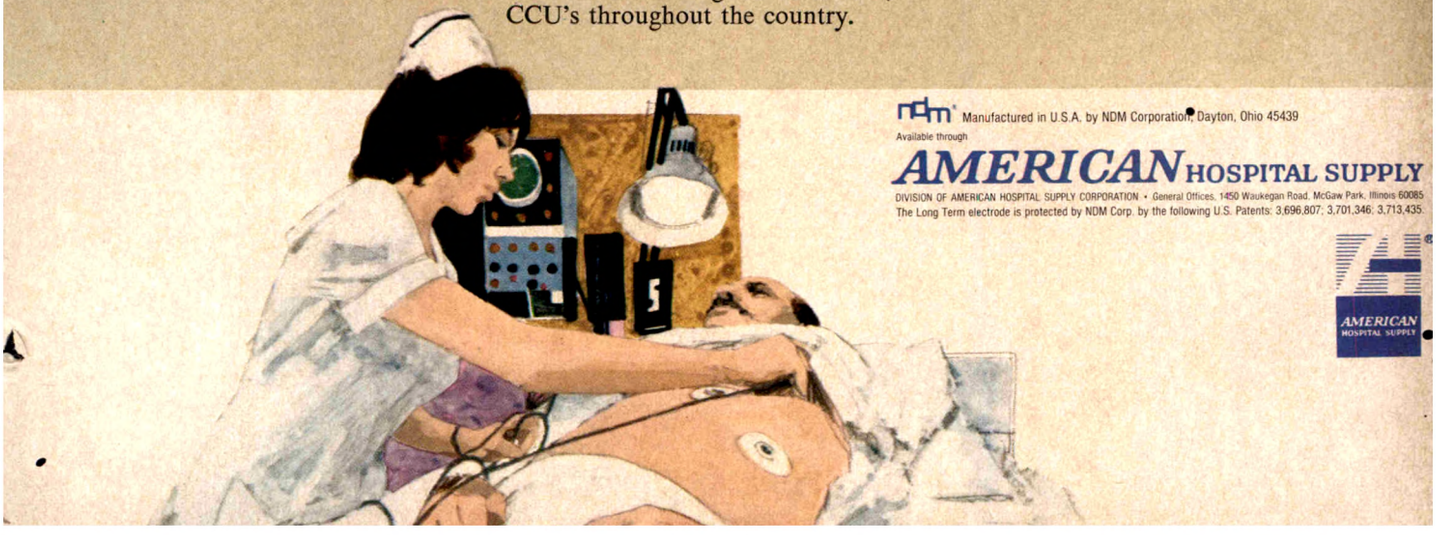

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The Long Term electrode is protected by NDM Corp. by the following U.S. Patents: 3,696,807; 3,701,346; 3,713,435.

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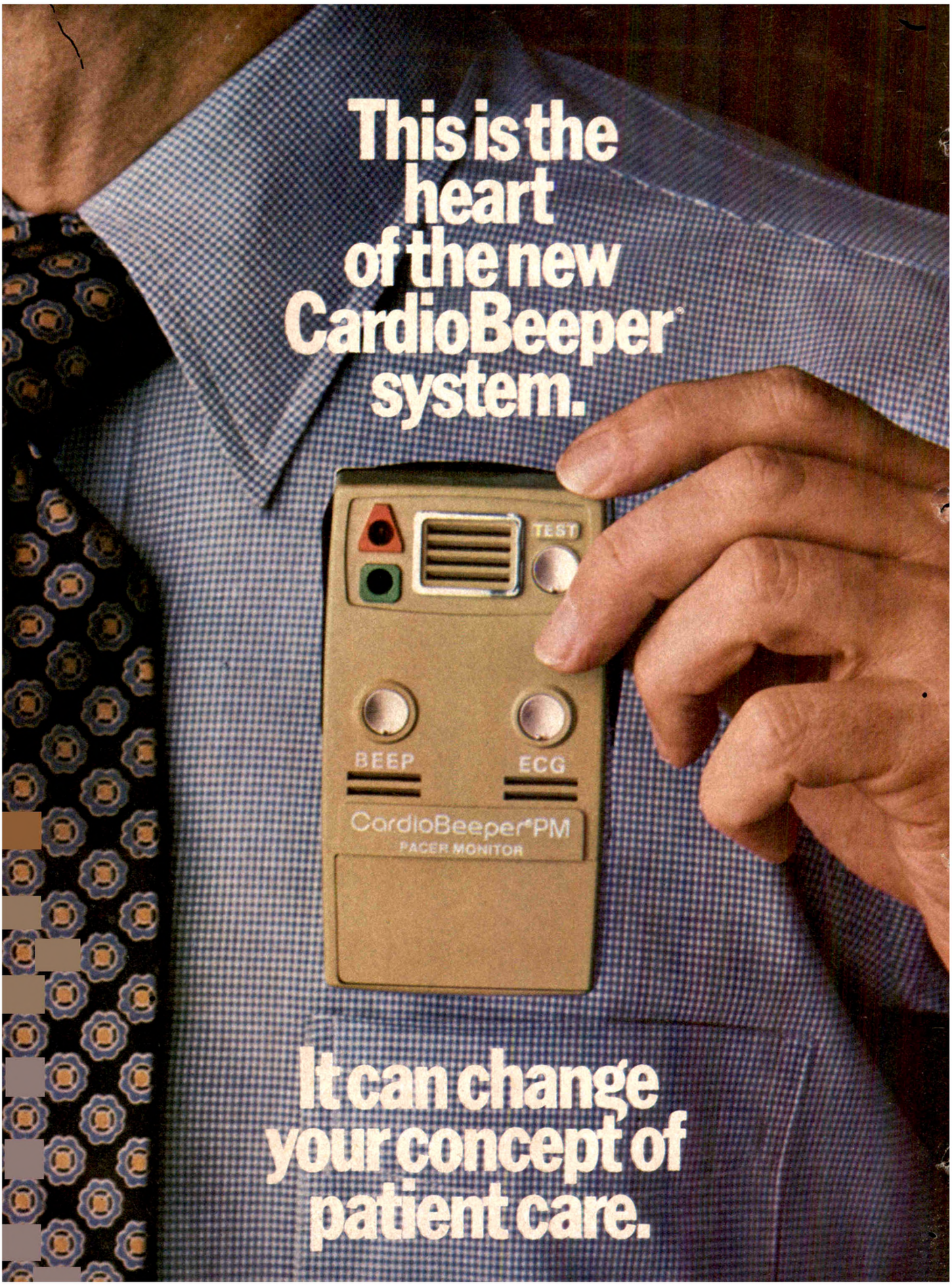
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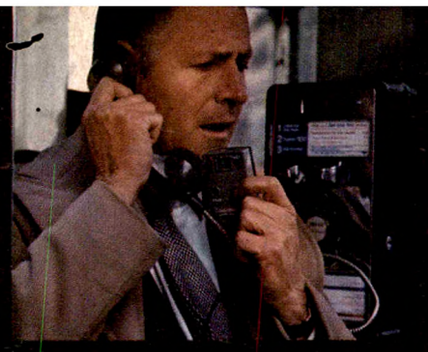
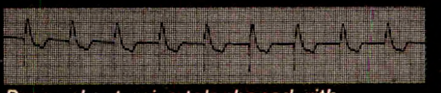
CardioBeeper® PM
PACER MONITOR
It can change your concept of patient care.



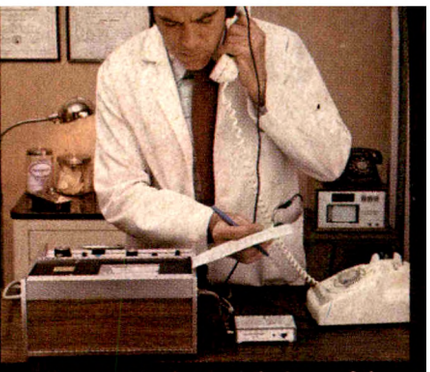
CardioBeeper®-PM pacer monitor are unlike any heart monitoring instruments now in use. They're five ounces, pocket-sized and relatively inexpensive. Yet they are unparalleled in electronic sophistication. The CardioBeeper monitors are engineered to permit your coronary patient, within seconds, to telephonically transmit his heart rate and rhythm or ECG. And to allow your pacemaker patient to transmit pacemaker rate interval and artifact, as well as confirmation of battery integrity and ventricular capture. At any time. From any conventional telephone. If indicated, you are then able to institute immediate, often life-sustaining action.



Pacemaker tracing telephoned with CardioBeeper-PM.

Normal ECG tracing telephoned with CardioBeeper.

The CardioBeeper system is simple to use. Your patient need not undress. Or be bothered with paste, gels or straps. He simply places a reusable electrode in each bare armpit. And to transmit, he merely holds the CardioBeeper



monitor next to the mouthpiece of the phone while touching a button. *Physician and patient stay in constant voice contact while sending and receiving.*

You can immediately receive the telephoned data as a series of audible "beeps" indicating each QRS complex or pacemaker spike. To receive a permanent record of ECG or pacemaker artifact, just connect a CardioBeeper® ECG Decoder to your telephone and to any conventional ECG machine. Or instead, connect a CardioBeeper® Decodalyzer to your phone to obtain a visual readout of heart rate or pacemaker rate in BPM, interval count in msec. or a direct ECG tracing for your records.

In life-threatening emergencies or routine checks, no remote cardiac monitoring instruments available today at any cost can rival the revolutionary CardioBeeper system. For further information, simply contact your Wyeth representative or Wyeth Laboratories, Box 8299, Philadelphia, Pa. 19101.

Manufactured for Wyeth Laboratories by Survival Technology, Inc.

CardioBeeper®-PM
pacer monitor
CardioBeeper®
heart monitor

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Clinically proven.

Model 8114

Edwards Laboratories presents a whole new case for the STARR-EDWARDS™ Cardiac Pacer: the Model 8116 Hermetically Sealed Ventricular Tracking Pulse Generator.

This second-generation pulse generator utilizes the same electronic circuit design of the Model 8114, which has attained a record of reliable clinical performance in more than 3,000 confirmed implants.

Of most significance, the Model 8116 features a hermetically sealed metal case to protect **the entire** electronic circuit and power supply from body fluid infiltration. Critical components function in a totally dry environment, thereby contributing toward improved reliability and longer operating life.

Further, the all-metal surface offers added external shielding against electromagnetic interference. Haynes Alloy 25, a biologically compatible material, covers the entire surface, obviating the need for an epoxy barrier. Case width is reduced to 2.0 cm., thereby contributing to an improved cosmetic appearance.

Inside the pulse generator,

Hermetically sealed.

Model 8116

improved RM-1 Mallory Mercury Cells are employed. Pacing rates of 70, 78 and 85 BPM may be selected as standard. Fixed rate versions are also available.

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For complete details, clinical data, and a description of Edwards' complete Cardiac Pacer System, please contact Edwards Laboratories, 17221 Red Hill Avenue, P.O. Box 11150, Santa Ana, California 92711, 714/557-8910, Cable: EDSLAB, Telex: 68:5567.

EDWARDS LABORATORIES®

Division of American Hospital Supply Corporation

If psychic tension interferes with cardiac rehabilitation, here's how Valium® can help.
(diazepam)

During hospitalization, Valium (diazepam) can relieve psychic tension that can disrupt bed rest and interfere with the rehabilitation program.

After the MI patient is stabilized, a certain amount of psychic tension is to be expected. Your reassurance, counseling and enlistment of family support can often minimize its effects. However, in some instances, the patient's thoughts may dwell constantly on his condition and how it will affect his life, thus producing excessive psychic tension that may present special problems. He may feel overwhelmed and be so burdened by these tensions that he is unable to rest and unable or unwilling to begin a program of rehabilitation. Under these circumstances, Valium® (diazepam) can often be a beneficial adjunct.

Valium can calm the cardiac patient and help reduce his psychic tension to appropriate levels. Valium is used with most classes of primary medications such as cardiac glycosides, diuretics, vasodilators, anticoagulants, anticholinergics and antacids. Careful consideration should be given to the pharmacology of agents used with Valium, particularly those which may potentiate its action.

During convalescence at home, Valium (diazepam) can reduce excessive anxiety that may hinder participation in active rehabilitation.

Your counseling and the family's support do much to control the anxieties that may interfere with this stage of convalescence—a time when you may wish to encourage a gradual increase in activity. But in some patients, excessive anxiety may retard general progress. For them, Valium can be beneficial during the post-hospital transition to full ambulation. And, because the convalescent cardiac patient may be particularly prone to excessive tension and anxiety at bedtime, the addition of an *h.s.* dose of Valium to the *b.i.d.* or *t.i.d.* schedule can reduce these symptoms and thus may encourage sleep. Therapy with Valium should be discontinued when symptoms have been reduced to tolerable levels.

What an informed cardiac patient should know about Valium therapy.

The cardiac patient should know that he can generally expect Valium to help relax and calm him so that he won't feel so overwhelmed by his tension and anxiety. An explanation of the importance of the dosage regimen you prescribe may go a long way to ensure his cooperation. As with all CNS-acting agents, the patient taking Valium should be cautioned against driving or operating dangerous machinery.

Valium® (diazepam)

2-mg, 5-mg, 10-mg tablets can relieve the cardiac patient's undue psychic tension

ROCHE

For a summary of product information, see the following page.

Valium® (diazepam)
2-mg, 5-mg, 10-mg tablets

can relieve the cardiac patient's undue psychic tension

Prompt and Effective Response Valium acts promptly to help relieve psychic tension in the cardiac patient.

Wide Margin of Safety At recommended dosages, oral Valium is generally well tolerated and does not significantly affect respiration, pulse or heart rate.

Flexible Dosage Available as *scored* tablets, oral Valium allows dosage to be easily readjusted to suit patients' changing needs.

Predictable Pharmacokinetically Pharmacokinetic studies of Valium demonstrate a highly predictable pattern of absorption, distribution, metabolism and excretion.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

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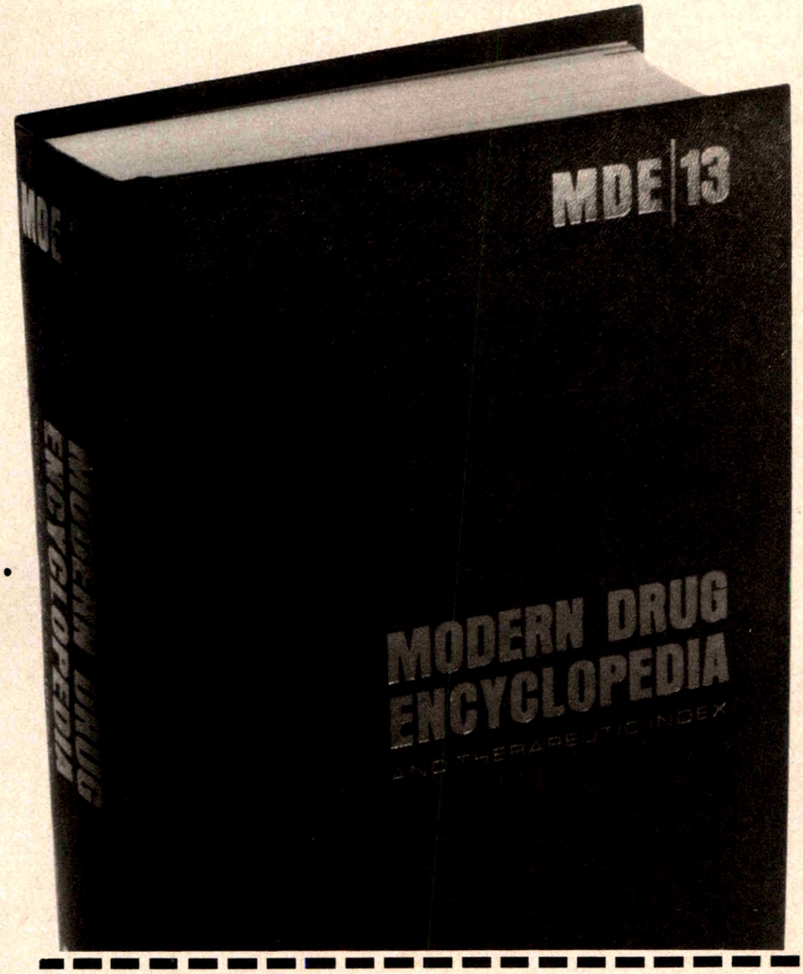

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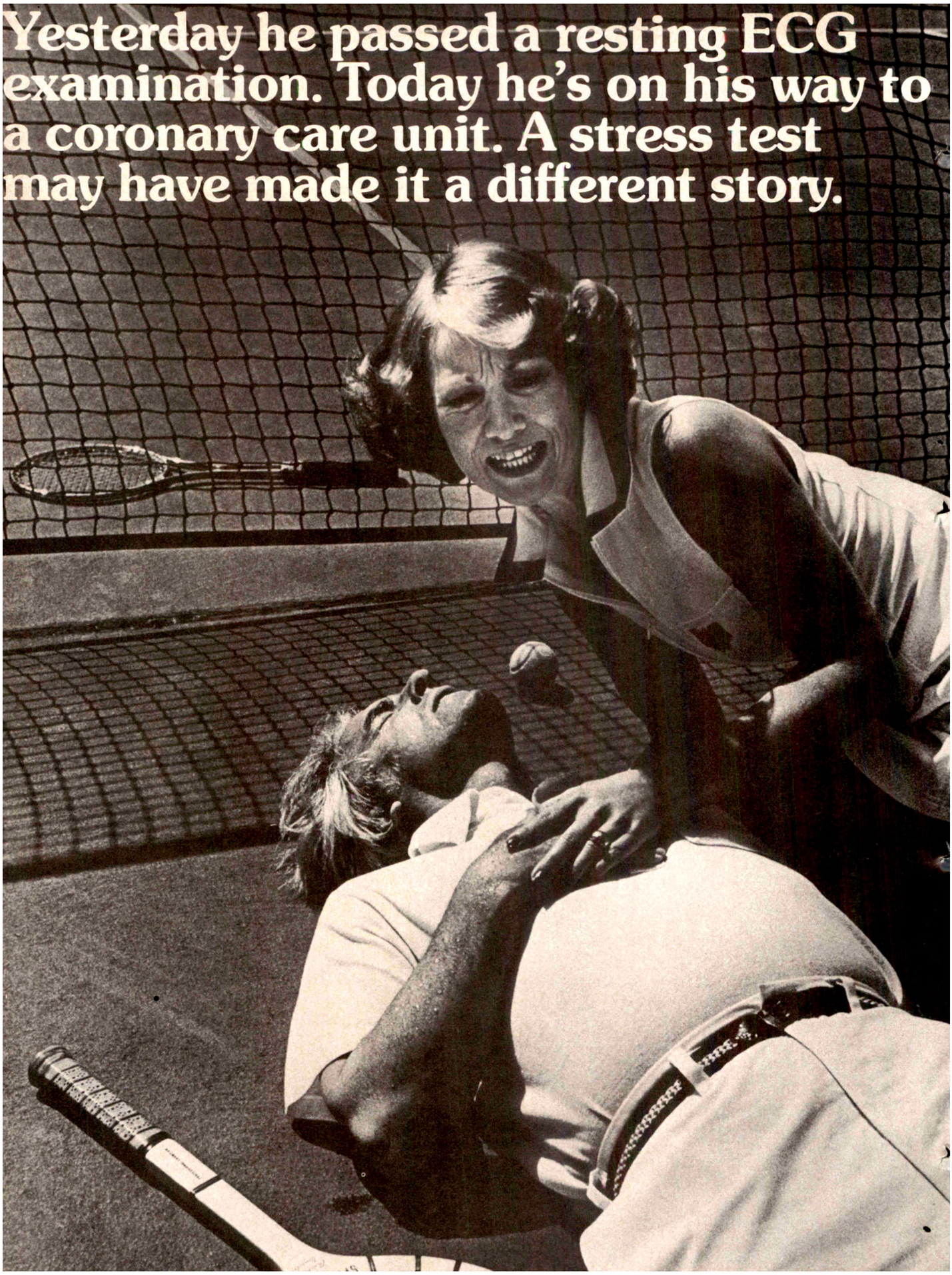
Yesterday he passed a resting ECG examination. Today he's on his way to a coronary care unit. A stress test may have made it a different story.

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Multi-lead exercise ECG system includes 2-channel scope, recorder, and heart rate meter.

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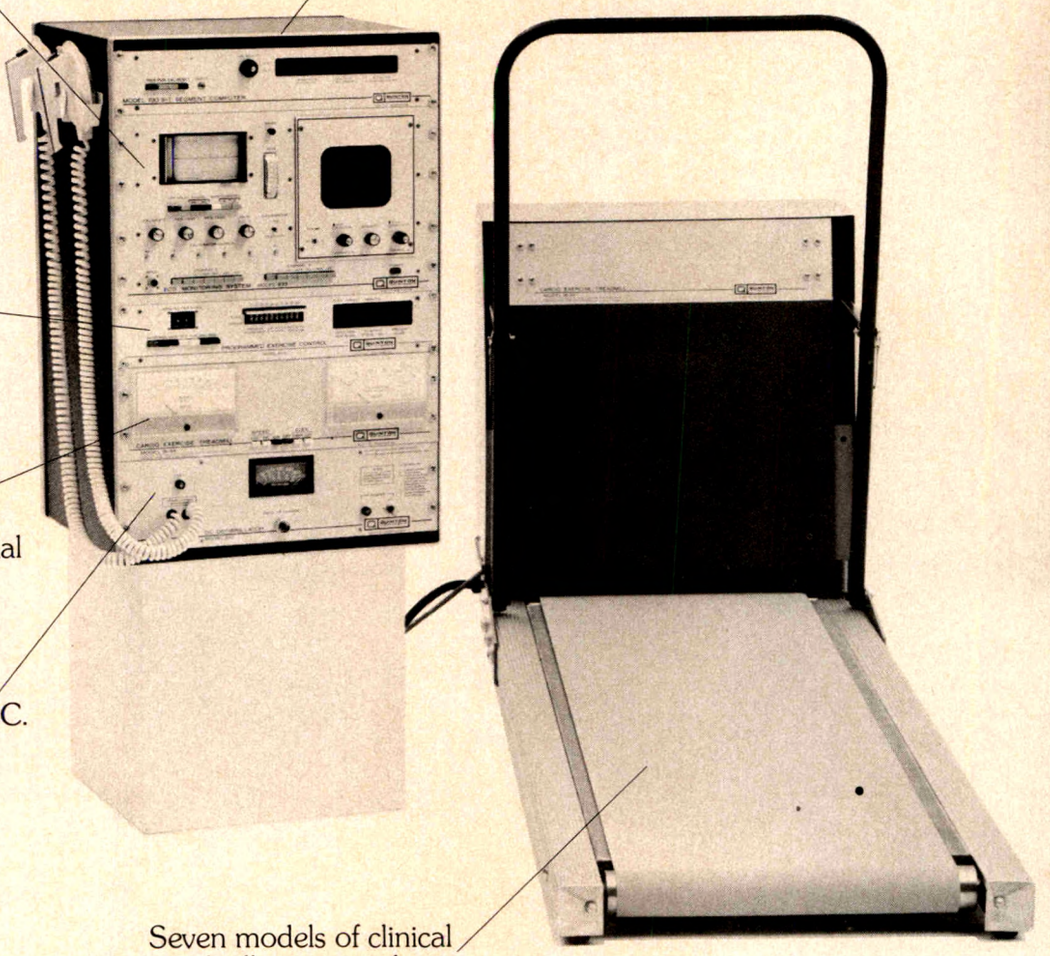
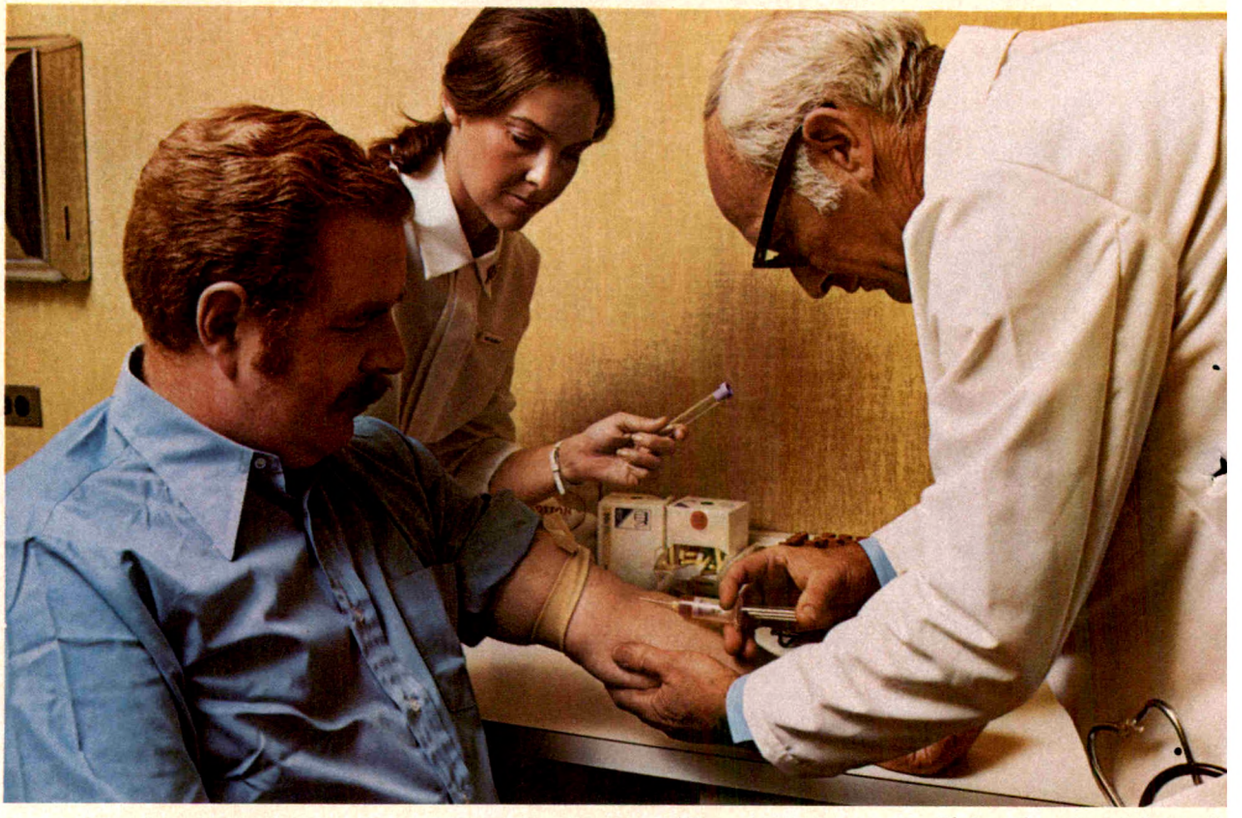


Seven models of clinical treadmills permit selection of the correct machine to match your requirements.

"Hyperlipidemia is one of several factors I search



(Photographs professionally posed.)

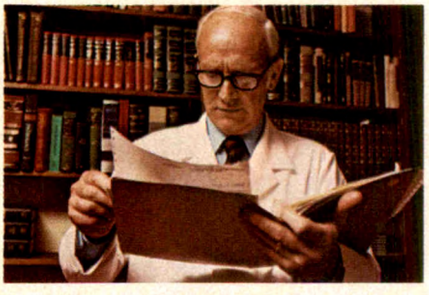
Complete lipid work-up should include both cholesterol and triglyceride determinations

Testing for both lipids—rather than just for cholesterol alone—increases the chances of detecting hyperlipidemia from 60% to over 95%.[2]

Lab results indicate pattern of lipid abnormality

When initial determinations of fasting serum cholesterol and triglyceride levels indicate the presence of hyperlipidemia, the pattern of the lipid abnormality should also be determined.[3]

When lipid elevations are confirmed, underlying disease states that may alter lipid metabolism should be ruled out through history, physical examination, and appropriate laboratory tests. Effective treatment of these pathologic conditions, if they exist, will often return the elevated lipids to a normal range. In the absence of an underlying cause, elevated lipid levels indicate a primary hyperlipidemia.



Therapy begins–but does not necessarily end–with specific dietary recommendations

Diet (specific for the lipid abnormality) is the starting point in the management of primary hyperlipidemia, and in the relatively rare Type I hyperlipoproteinemia it is the *only* therapy since currently available drugs are ineffective. But in the drug-responsive types (Types IIa, IIb, III, IV and V) diet alone may fail to lower lipids adequately.

Drug therapy is often necessary as an adjunct to diet

Convincing the asymptomatic hyperlipidemic patient to give up his favorite foods for benefits he may not feel is, at best, a difficult task. Even under carefully monitored dietary regimens, lipid reductions may be inadequate.[4] For these reasons it is often necessary to add an antilipemic agent to the dietary regimen to produce a significant reduction in serum lipids.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

for and vigorously treat."[1]

"Along with early hypertension, excessive cigarette smoking and dietary indiscretions, it is one of the few manifestations of modern society that an individual physician can attempt to control."[1]

This is how one clinician views hyperlipidemia—a condition widespread in America today. The treatment he speaks of often calls for a dietary regimen specific for the lipid abnormality *plus* an antilipemic agent. And since many hyperlipidemic patients exhibit elevations of *both* cholesterol and triglycerides, they need a drug such as ATROMID-S (clofibrate), which has the ability to lower *both* lipids.

Atromid-S significantly reduces cholesterol and triglycerides—often in patients unresponsive to diet[5]

ATROMID-S as an adjunct to diet has a proven record of effectiveness in lowering serum elevations of both cholesterol and triglycerides.[5-8]

Although most hyperlipidemic patients are asymptomatic, a small number may exhibit skin lesions or xanthomas. Regression of xanthomatous lesions with ATROMID-S visually demonstrates the efficacy of this lipid-lowering agent. In some patients xanthomas disappear completely. In others the size and number of lesions are reduced.

Continuous treatment, maintenance of daily dosage vital to long-term control

Reliable cholesterol- and triglyceride-lowering effect is usually sustained as long as ATROMID-S treatment is uninterrupted. This ability to maintain control of serum lipids for extended periods is of primary importance in treating a disorder as persistent as hyperlipidemia.

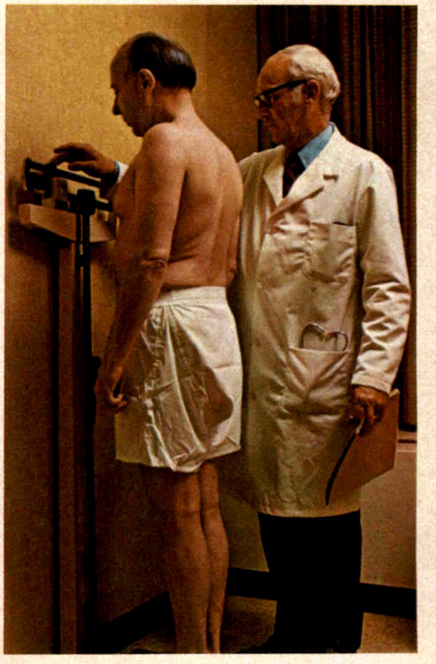
ATROMID-S is effective in a simple, well-accepted regimen that patients can stay with. Initial *and* maintenance dosage is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage. To maintain continuous control of lipid levels, therapy should be uninterrupted.

The lipid-lowering effect of ATROMID-S is usually noted during the first month of therapy. The higher the initial level, the greater the lipid reduction likely to occur.

If response is inadequate after three months of therapy, the drug should be discontinued. However, if xanthoma tuberosum is present, treatment should continue for longer periods (even up to one year) provided there is a reduction in the size and/or number of the xanthomas.

10 years of successful overall clinical experience with Atromid-S

Throughout more than ten years of widespread use, ATROMID-S has proven to be an effective and very well-tolerated drug. However, before prescribing, you should be thoroughly familiar with the possible adverse reactions as well as with the precautions and warnings described on the last page of this advertisement.



Periodic follow-up important

Once blood lipids have been stabilized at normal levels on a regimen of diet and ATROMID-S, the patient should be examined and his blood lipids tested every two to three months during the first year or so. If stabilization at such lower levels is maintained over this period, the intervals between measurements can be lengthened.

Atromid-S®

Brand of clofibrate

helps control the lipid factor in your patient's profile

Ayerst®

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

See last page of advertisement for prescribing information.

Atromid-S® (clofibrate)
helps reduce elevated cholesterol and/or triglyceride levels — not just cholesterol alone

Initial and maintenance dosage: 2 Gm. daily (four capsules), in divided doses. Some patients may respond to a lower dosage.

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® (clofibrate)

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage. *Maintenance:* Same as for initial dosage. **Note:** In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S (clofibrate). The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: **1.** La Bree, J., M.D. (Director of Medical Education, St. Mary's Hosp., Minneapolis, Minn.): Unraveling the Metabolic Mysteries Affecting Diagnosis and Therapy, Ayerst Laboratories, 1972, p. 13. **2.** Fredrickson, D. S., *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R.: Drugs Affecting Lipid Metabolism, New York, Plenum Press, 1969, vol. 4, p. 314. **3.** Levy, R. I., in Conn, H. F.: Current Therapy 1973, Philadelphia, Saunders, 1973, p. 267. **4.** Parsons, W. B., Jr.: Clin. Med. *78*:15 (Nov.) 1971. **5.** Gelfand, M. L., and Garber, M.: Exhibit, American College of Cardiology Meeting, New Orleans, La., Feb. 21-Mar. 1, 1970. **6.** Berkowitz, D.: J.A.M.A. *218*:1002 (Nov. 15) 1971. **7.** Zelis, R., *et al.*: J. Clin. Invest. *49*:1007 (May) 1970. **8.** Levy, R. I., and Fredrickson, D. S.: Am. J. Cardiol. *22*:576 (Oct.) 1968.

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On Reliability and a Pound of Flesh

The life's blood of an electrocardiograph is the chart that flows through it.

Assurance that the recording is totally reliable depends, in part, on the quality of the chart itself.

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Charts, as provided by others, are imitations at best. They may save a few pennies, but not without risk of shedding a "drop of reliability".

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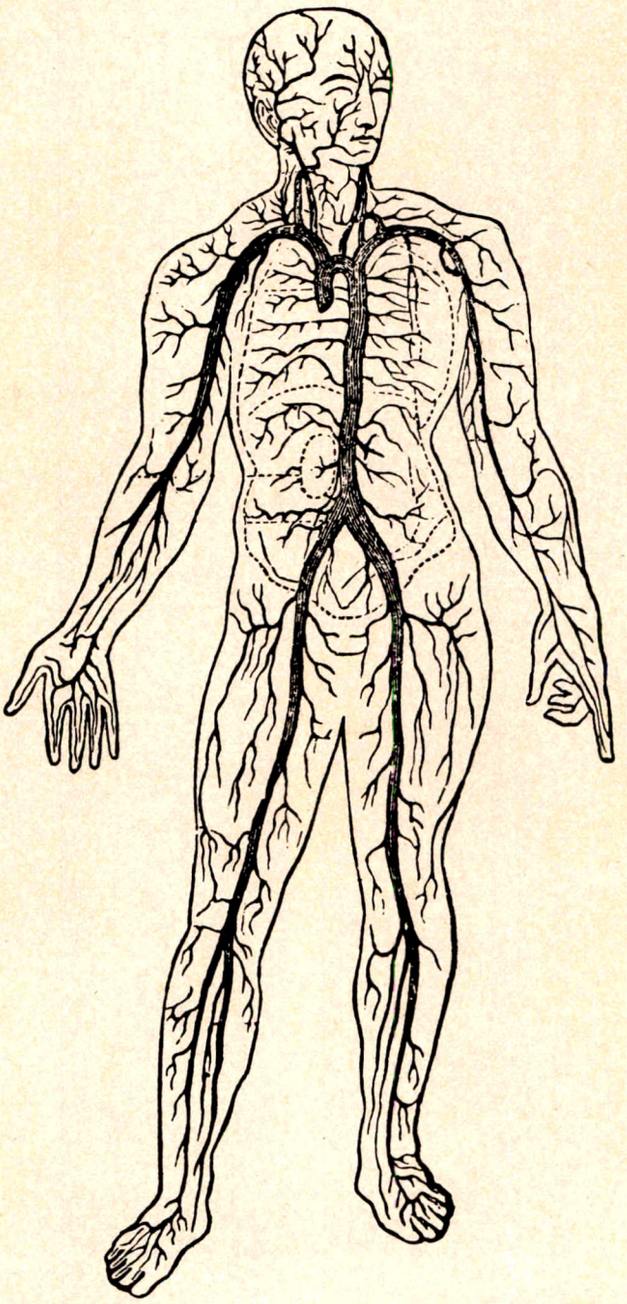
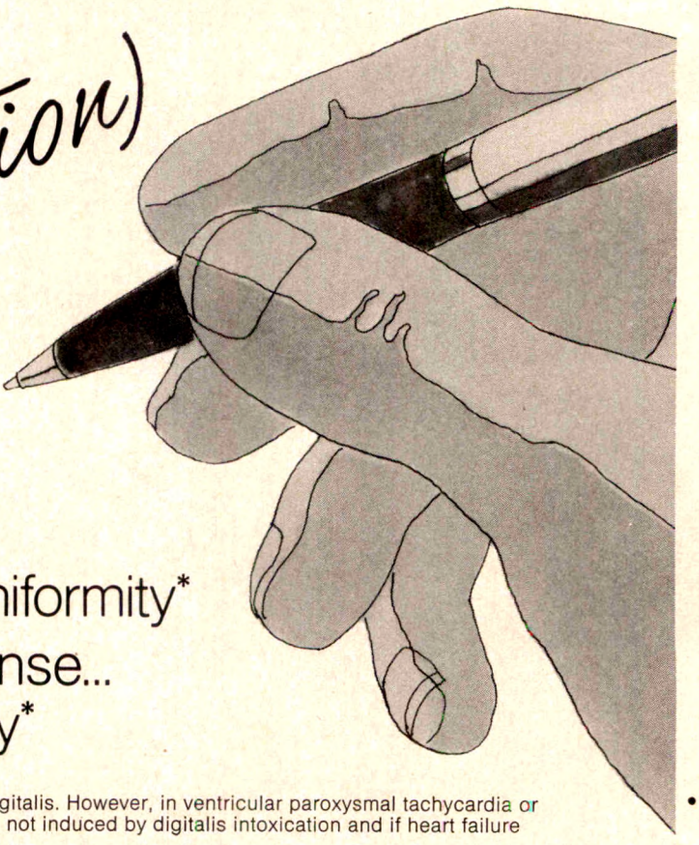


Lanoxin
[digoxin]
(no substitution)



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precision quality control...
- assured tablet content uniformity*

predictable patient response...
- proven biologic availability*

Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

LANOXIN® digoxin TABLETS. **0.125 mg.** (yellow) in bottles of 100 and 1,000. **0.25 mg.** (white) scored, in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack, strips of 10 tablets, 10 boxes of 100 tablets (1,000). **0.5 mg.** (green) scored, in bottles of 100 and 1,000.

Lanoxin® digoxin

*Complete literature available on request from Professional Services Dept. PML.

Wellcome / **Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

JULY 1975

The American Journal of CARDIOLOGY

VOLUME 36

NUMBER 1

CLINICAL STUDIES

Echocardiography in Acute Myocardial Infarction

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Indianapolis, Indiana

Sixty-four patients with acute transmural myocardial infarction had daily echocardiograms while in the coronary care unit. Patients with previous infarction were excluded. The electrocardiographic site of infarction was anterior wall in 28, inferior wall in 33 and both anterior and inferior wall in 3 patients. Echocardiograms satisfactory for interpretation were obtained in 92 percent of cases. Abnormal left ventricular wall motion corresponding to the electrocardiographic site of infarction was seen in the echocardiogram in 84 percent of cases. Exaggerated normal motion in noninfarcted areas was seen in 30 percent. The left ventricular internal dimension correlated with clinical heart failure ($P < 0.005$) and was increased in 50 percent. Abnormal mitral valve closure, which reflects increased left ventricular end-diastolic pressure, was present in 33 percent. This finding did not correlate significantly with clinical heart failure. By combining the measurements of left ventricular internal dimension and mitral valve closure, it was possible to predict hospital mortality from the echocardiograms. The results indicate that echocardiography is a useful technique in the study and management of patients with acute myocardial infarction.

From the Krannert Institute of Cardiology and the Department of Medicine, Indiana University School of Medicine, Indianapolis, Ind., and the Hendricks County Hospital, Danville, Ind. This study was supported in part by the Herman C. Krannert Fund, Indianapolis, Ind.; by Grants HL-06308, HL-05363 and HL-05749 from the National Heart and Lung Institute of the National Institutes of Health, Bethesda, Md.; by the Indiana Heart Association, Indianapolis, Ind.; and by a Grant-in-Aid from the American Heart Association, Northeast Indiana Chapter, Inc., Indianapolis, Ind. Manuscript accepted December 11, 1974.

Address for reprints: Betty C. Corya, MD, Indiana University Medical Center, 1100 West Michigan St., Indianapolis, Ind. 46202.

Although present echocardiographic techniques do not permit identification of echoes from the coronary arteries and, therefore, direct assessment of the presence and severity of coronary artery disease, some of the important consequences of coronary artery disease may be indirectly evaluated by examination of the left ventricle.[1–9] Most previous studies have dealt with abnormalities of wall motion[1–3] and left ventricular volume[4–6] in patients with chronic coronary artery disease. Less information is available on the use of echocardiography in patients with acute infarction. Change in motion of the posterior left ventricular wall has been shown in animals with experimental infarction of the posterior wall.[7,8] These changes in posterior wall motion were presumed to be due to segmental left ventricular dysfunction since they were not seen in dogs with apical infarction.[8] In addition, decreased posterior wall velocity has been demonstrated in patients with inferior as opposed to anterior infarction,[9] and abnormal

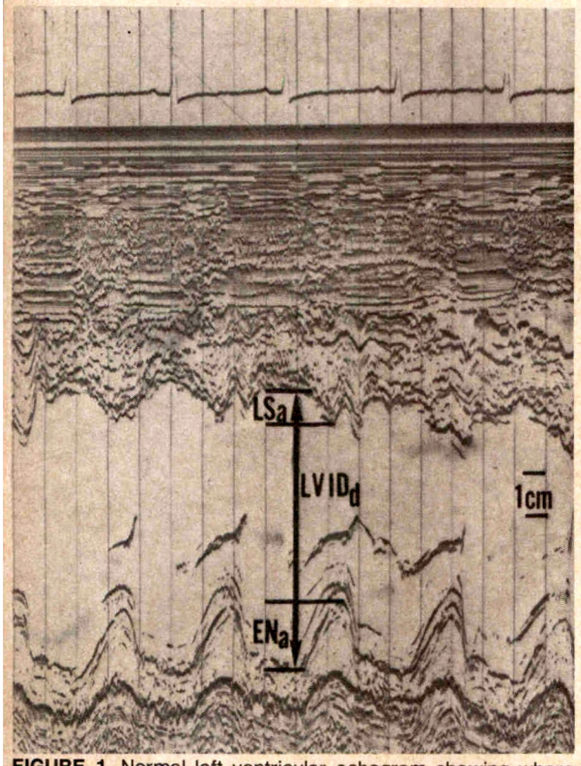

FIGURE 1. Normal left ventricular echogram showing where measurements were made. EN_a = amplitude of endocardial echocardiographic motion; LS_a = amplitude of left septal echocardiographic motion during ejection; $LVID_d$ = left ventricular internal dimension at end-diastole.

anterior left ventricular wall motion has been demonstrated in patients with transmural anterior infarction.[2] Good correlation has been reported[10] between echocardiographic and dye-dilution methods of measuring cardiac output in nine patients with acute infarction.

Because of the noninvasive nature of echocardiography and its potential usefulness in assessing both segmental and generalized left ventricular function, investigation into its use in acute infarction is indicated. Among the many questions that need to be asked are: (1) How often can technically satisfactory echocardiograms be obtained in patients with acute myocardial infarction; (2) what are the incidence rates and sites of abnormal left ventricular echocardiographic motion, and what is its relation to the electrocardiographic site of infarction; (3) how soon after infarction do abnormalities of echocardiographic motion occur; (4) what is the relation of echocardiographic findings to clinical heart failure; and (5) are echocardiographic measurements helpful in predicting mortality in acute infarction? This report deals with these questions.

Methods

Patients: Clinical and echocardiographic data were collected from 64 consecutive patients with acute transmural myocardial infarction. Patients with a history of previous myocardial infarction were excluded. All patients were examined daily by the same investigator and were included

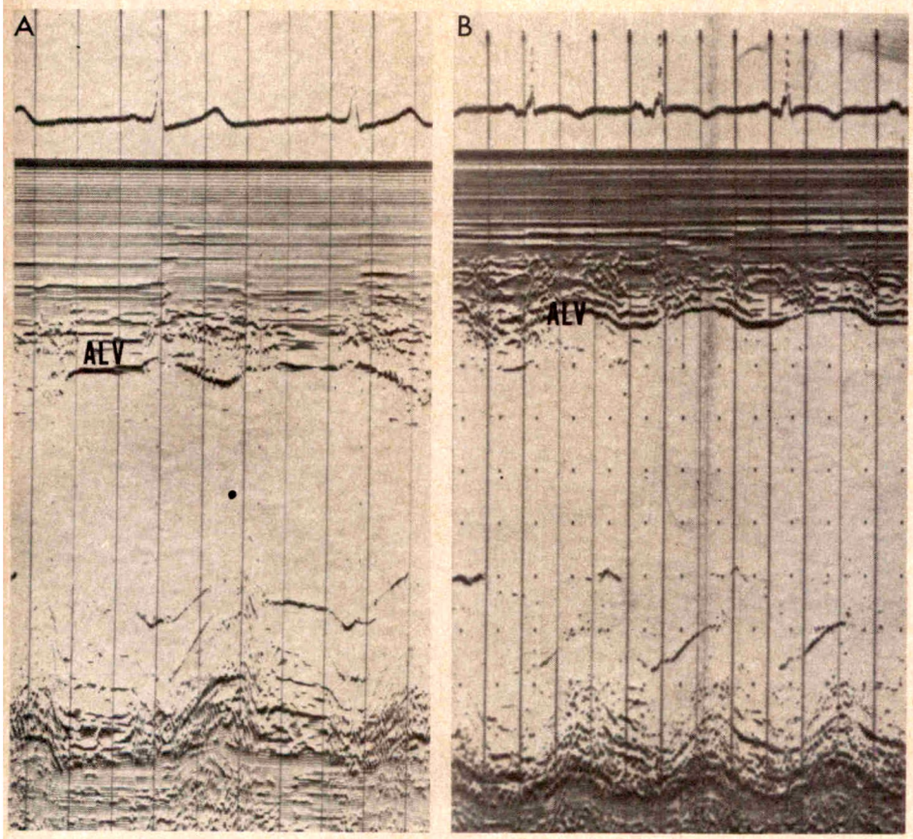

FIGURE 2. Left ventricular echograms recorded with the transducer overlying the anterior left ventricular wall (ALV). **A,** normal subject. The motion is away from the chest wall (normal) during ejection. **B,** from a patient with acute anterior wall myocardial infarction. The anterior left ventricular wall motion during ejection is paradoxical.

only if diagnostic electrocardiographic changes (Q wave greater than 0.04 second) of transmural infarction plus typical chest pain or a characteristic curve of serum enzyme activity, or both, was present. A diagnosis of congestive heart failure was made when the patient manifested bilateral basilar rales that did not clear with coughing or a third sound gallop, or both, consistent with the Killip classification.

Echocardiograms: Echocardiograms were obtained at the bedside as often as possible—in most cases daily—while the patients were in the coronary care unit. A Smith-Kline echograph with a 2.25 megahertz transducer 1.25 cm in diameter and collimated at 7.5 cm was used to obtain echoes. M mode tracings were made with a portable Honeywell Model 1856 strip chart recorder. A simultaneous electrocardiographic monitoring lead was recorded on each tracing.

Echoes were first recorded from the mitral valve. From that position a sector scan of the left ventricle from base to apex was recorded, as previously described,[11] in more than one interspace when possible. The transducer was then moved laterally 5 to 7.5 cm across the chest to record echoes from the anterior left ventricular wall. Details of this technique have previously been described.[2]

Echocardiographic measurements: The echocardiograms were interpreted without knowledge of the clinical information. Figure 1 illustrates a normal left ventricular echogram and shows where the measurements used for analysis were made. The left ventricular internal dimension at end-diastole ($LVID_d$) was taken at the peak of the R wave in the electrocardiogram at about the level of the posterior leaflet of the mitral valve. This was divided by the body surface area to obtain an $LVID_d$ index. The normal $LVID_d$ index in our laboratory is 3.2 cm/m^2 or less. The amplitude of left septal and left endocardial echocardiographic motion during ejection was measured at or just below the posterior mitral valve leaflet. Normal septal motion in our laboratory ranges from 0.3 to 0.8 cm (mean 0.6) and normal endocardial amplitude ranges from 0.8 to 1.6 cm (mean 1.3). Paradoxical septal motion was given a value of 0. Motion of both the septum and endocardium at the apex was also observed.

The anterior left ventricular wall echo was called normal if it moved away from the transducer during ejection and abnormal if it was flat or moved toward the transducer during ejection. (Fig. 2, A and B)

The period of mitral valve closure (A-C interval) was measured from the peak of the *A* wave in the mitral echogram to the point where the echoes from the anterior and posterior mitral leaflets met (Fig. 3). Abnormal mitral valve closure, which has been shown to be associated with increased left ventricular end-diastolic pressure,[12] was defined as a P-R minus duration of mitral closure (PR-AC) interval of 0.06 second or less. The duration of mitral valve closure is subtracted from the P-R interval in the electrocardiogram since the time between atrial and ventricular contraction also affects mitral valve closure.[13,14] As the mitral valve closure time increases, presumably because of increased left ventricular pressure, the PR-AC interval decreases if the P-R interval remains constant.

Statistical analysis: Data were analyzed by the Student *t* test. Chi square analysis was used to find if there was a relation between the echocardiographic measurements and congestive heart failure and to determine the ability of the following variables and combinations of variables to predict mortality on admission and at the time of the last echocardiogram (excluding admission echocardiogram): (1) elevated $LVID_d$ index; (2) abnormal mitral valve closure reflecting increased left ventricular end-diastolic pressure; (3) elevated $LVID_d$ index plus abnormal mitral valve closure; (4) $LVID_d$ index/PR-AC ratio as a volume/pressure ratio; and (5) abnormal wall motion.

Clinical variables analyzed by the same statistical methods were (1) age greater than 60 years; (2) sex; (3) serum glutamic oxaloacetic transaminase level greater than 250 units; (4) location of infarction; (5) third sound gallop; (6)

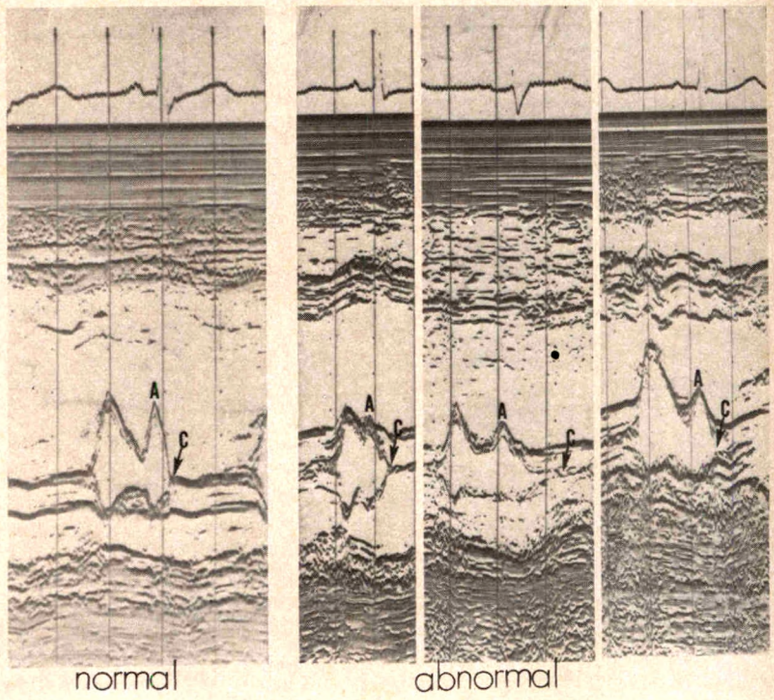

FIGURE 3. Mitral valve echograms showing abnormal mitral valve closure (P-R interval of electrocardiogram minus A-C interval = 0.06 second or less). The configuration of the A-C echo is variable. A = point at which the mitral valve begins to close; C = point of complete closure of the mitral valve.

TABLE I

Echocardiographic Data

		Electrocardiographic Site of Transmural Infarction		
	Normal (17 cases)	Anterior (28 cases)	Inferior (33 cases)	Both (3 cases)
LSa (cm)				
Measured (no.)	17	25	31	3
Range	0.3–0.8	0–.6	0–2.0	0–1.1
Mean	0.63	0.08	0.81	0.37
P value		<0.001	<0.025	NS
no. abn (<0.3)		20 (80%)	1 (3%)	2 (66%)
(>0.8)		None	12 (39%)	1 (33%)
ENa (cm)				
Measured (no.)	17	25	28	3
Range	0.8–1.6	0.8–2.1	0–1.7	0–1.3
Mean	1.29	1.40	0.66	0.60
P value		NS	<0.001	<0.001
no. abn (<0.8)		None	16 (57%)	2 (66%)
(>1.6)		4 (16%)	2 (7%)	None
ALV				
Recorded (no.)		17	21	3
no. abn		13 (76%)	1 (5%)	3 (100%)
$LVID_d$ index (cm/m²)				
Measured (no.)	17	27	31	3
Range	2.2–3.3	1.9–4.4	2.4–4.3	2.9–3.7
Mean	2.8	3.3	3.0	3.4
P value		<0.001	<0.05	<0.05
no. abn (>3.2)	1	19 (70%)	11 (35%)	2 (66%)
MV closure				
Measured (no.)		22	22	3
no. abn PR-AC (≤0.06 second)		11 (50%)	9 (41%)	1 (33%)

abn = abnormal; ALV = anterior left ventricular wall echo; ENa = amplitude of endocardial echocardiographic motion; LSa = amplitude of left septal echocardiographic motion during ejection; $LVID_d$ index = left ventricular internal dimension at end-diastole/body surface area; MV = mitral valve; *P* = probability. PR-AC = P-R interval from the electrocardiogram minus the A-C interval from the mitral valve echogram.

bilateral rales; and (7) presence of heart failure on the basis of the Killip classification.

Results

Clinical Data

The 64 patients ranged in age from 31 to 85 years (mean 60) and included 36 men and 28 women. Congestive heart failure was present during the first 48 hours in 58 percent (37 of 64), and 4 patients had pulmonary edema and 2 had shock on admission. The hospital mortality rate for the entire group was 23 percent (15 of 64). The electrocardiographic site of infarction was anterior wall in 28, inferior wall in 33 and both anterior and inferior wall in 3 patients.

The group of 28 patients with anterior wall infarction included 17 men and 11 women whose ages ranged from 40 to 82 years (mean 60). Congestive heart failure was present within 48 hours of admission in 64 percent (18 of 28), and the hospital mortality rate was 32 percent (9 of 28). The 33 patients with inferior wall infarction included 16 men and 17 women whose ages ranged from 31 to 85 years (mean 59). Fifty-two percent of these patients (17 of 33) had congestive heart failure within 48 hours and the hospital mortality rate was 15 percent (5 of 33). The three patients with both anterior and inferior wall infarction were men aged 51 to 66 years (mean 58). Two had congestive heart failure, and one died in the hospital.

Echocardiographic Data

Echocardiographic data for the three groups are presented in Table I. The most obvious echocardiographic abnormalities were those of left ventricular wall motion. Decreased or paradoxical echocardiographic motion was found on admission in 84 percent of patients (54 of 64) with acute transmural infarction. The echocardiograms in Figures 4 and 5, obtained from two patients in this study, demonstrate, respectively, abnormal septal and posterior wall motion. In 73 percent of patients (47 of 64) abnormal motion was seen at the "base" of the heart where the ultrasonic beam traverses the mitral valve and where standard left ventricular echocardiographic measurements are made. In four instances the abnormality was seen only at the apex, and in three cases only the anterior left ventricular wall was abnormal. "Exaggerated normal" motion in areas not involved electrocardiographically was seen in 30 percent of this series of patients. The area of decreased or paradoxical motion corresponded to the electrocardiographic site of infarction with two exceptions. One patient with inferior wall infarction had abnormal anterior left ventricular wall motion as well as decreased endocardial motion, and another with only inferior wall infarction electrocardiographically had absence of septal motion at the base of the heart in addition to abnormal endocardial motion.

The abnormal motion associated with acute infarction was nearly always seen in the admission echocardiogram, and very little daily change was seen in subsequent tracings in the coronary care unit. Although it was not possible to quantitate the area of abnormal contraction, the changes appeared to be greater and more extensive than those we have observed in patients with chronic coronary artery disease; preliminary observations in follow-up tracings (3 to 6 months) indicate that some improvement occurred later.

Patients with anterior wall infarction: Left septal echoes were adequate for measuring amplitude of motion during ejection in 25 of the 28 patients with electrocardiographic evidence of anterior myocardial infarction. Eighty percent (20 of 25) had abnormally decreased motion (less than 0.3 cm) with a mean of 0.08 cm (range 0 to 0.6) that was significantly different from normal ($P < 0.001$). The endocardial amplitude was also measurable in 25 patients, and the group mean was not significantly different from normal. Four patients had endocardial amplitude values above the normal range (0.8 to 1.6 cm). Anteri-

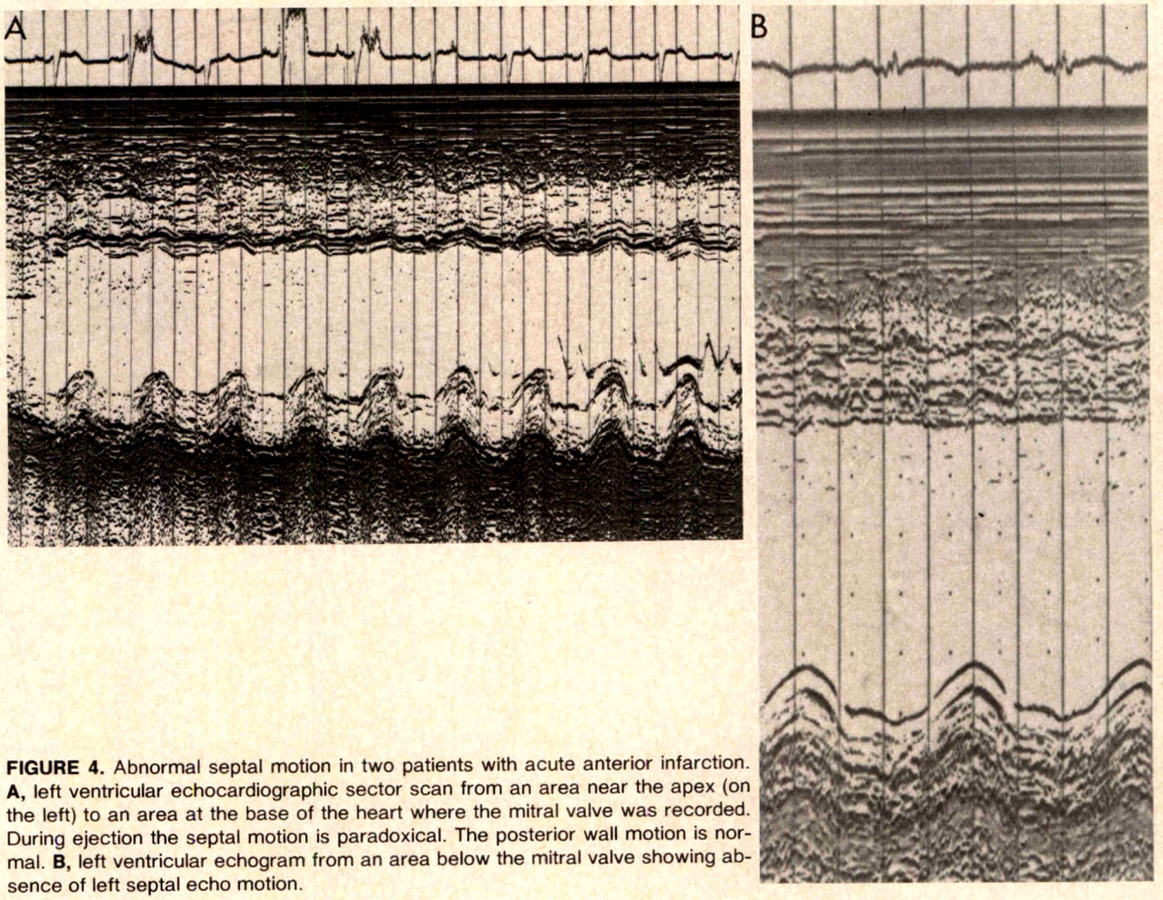

FIGURE 4. Abnormal septal motion in two patients with acute anterior infarction. **A,** left ventricular echocardiographic sector scan from an area near the apex (on the left) to an area at the base of the heart where the mitral valve was recorded. During ejection the septal motion is paradoxical. The posterior wall motion is normal. **B,** left ventricular echogram from an area below the mitral valve showing absence of left septal echo motion.

or left ventricular echocardiographic motion was abnormal in 76 percent (13 of 17) of those in whom it was recorded.

The left ventricular internal dimension at end-diastole ($LVID_d$) index was elevated in 70 percent (19 of 27) of these patients, and 50 percent (11 of 22) of them had abnormal mitral valve closure.

Patients with inferior wall infarction: Left septal echoes could be measured in 31 of 33 patients with inferior wall infarction. Values ranged from 0 to 2.0 cm (mean 0.81). The left septal amplitude was less than normal in only 1 patient and was greater than normal in 12 patients ($P < 0.025$). Endocardial amplitude ranged from 0 to 1.7 cm (mean 0.7), with 2 patients having values greater than normal and 16 having values below the normal range ($P < 0.001$). Anterior left ventricular wall motion was abnormal in 1 of the 21 patients in whom it was recorded. The left ventricular internal dimension index was elevated in 35 percent (11 of 31), and abnormal mitral valve closure was present in 41 percent (9 of 22) of these patients.

Patients with both anterior and inferior wall infarction: Measurements in the three patients with both anterior and inferior electrocardiographic changes showed septal motion increased in one and decreased in two, endocardial motion decreased in two, anterior left ventricular echo motion abnormal in three, left ventricular internal dimension index el-

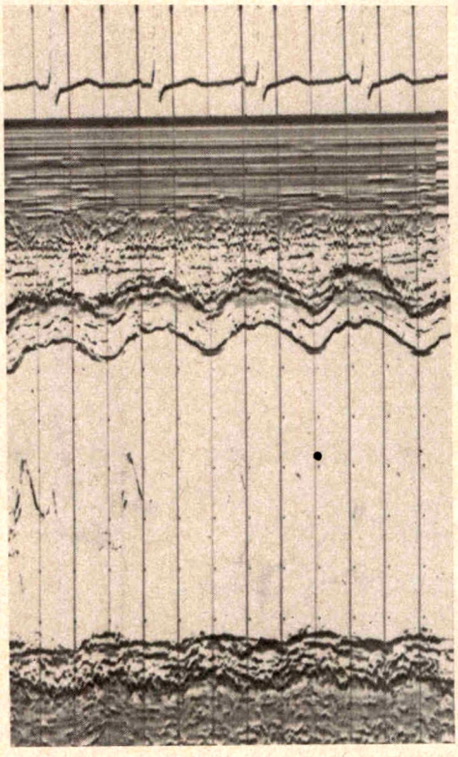

FIGURE 5. Left ventricular echogram from a patient with acute inferior wall infarction showing greatly decreased posterior wall motion and normal septal motion.

TABLE II

Analysis of Echocardiographic Measurements in Predicting Mortality in Acute Myocardial Infarction

Measurement	Echocardiogram	Patients Examined (no.)	Patients in Whom Value Could be Measured		Patients with Normal Value		Patients With Abnormal Value		*P* Value
			no.	Mortality	no.	Mortality	no.	Mortality	
$LVID_d$ index	First	64	61	15/61 (25%)	29	4/29 (14%)	32	11/32 (34%)	NS
	Last	40	40	7/40 (18%)	18	3/18 (17%)	22	4/22 (18%)	NS
MV closure (PR — AC)	First	64	47	9/47 (19%)	26	3/26 (12%)	21	6/21 (29%)	NS
	Last	40	35	7/35 (20%)	17	0/17	18	7/18 (39%)	<0.005
MV closure + $LVID_d$ index	First	64	46	9/46 (20%)	35*	3/35 (9%)	11*	6/11 (55%)	<0.001
	Last	40	35	7/35 (20%)	26	3/26 (12%)	9	4/9 (44%)	<0.05
$LVID_d$ index/ PR-AC	First	64	46	9/46 (20%)	33	3/33 (9%)	13	6/13 (46%)	<0.005
	Last	40	35	7/35 (20%)	27	1/27 (4%)	8	6/8 (75%)	<0.0001
LSa	First	64	59	15/59 (25%)	23	4/23 (17%)	36	11/36 (31%)	NS
	Last	40	38	8/38 (21%)	17	2/17 (12%)	21	6/21 (29%)	NS
ENa	First	64	56	14/56 (25%)	32	6/32 (19%)	24	8/24 (33%)	NS
	Last	40	35	5/35 (14%)	25	2/25 (8%)	10	3/10 (30%)	NS
ALV	First	64	41	10/41 (24%)	24	4/24 (17%)	17	6/17 (35%)	NS
	Last	40	20	2/20 (10%)	11	2/11 (18%)	9	0/9	NS

* Normal for this measurement refers to only one or neither value being abnormal; abnormal refers to both values being abnormal.
NS = not significant; other abbreviations as in Table I.

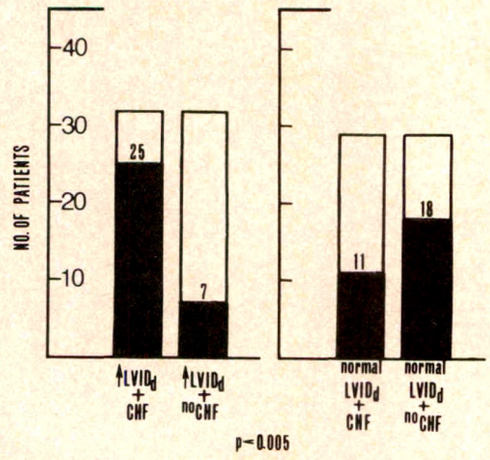

FIGURE 6. Relation of the incidence of elevated $LVID_d$ index to clinical congestive heart failure in patients with acute myocardial infarction. CHF = congestive heart failure; $LVID_d$ = left ventricular internal dimension at end-diastole/body surface area.

evated in two and abnormal mitral valve closure in one.

Echocardiographic Measurements and Clinical Heart Failure

Figure 6 shows the significant (P <0.005) correlation between echocardiographic left ventricular size on the admission echocardiogram and clinical heart failure based on the Killip classification. However, 38 percent of patients (11 of 29) with a normal left ventricular internal dimension had clinical heart failure and 22 percent (7 of 32) with an elevated left ventricular internal dimension had no clinical evidence of failure. There was also a significant correlation between an echocardiographically dilated left ventricle and the presence of either bilateral rales (P <0.005) or a third sound gallop (P <0.025).

There was no significant correlation between abnormal mitral valve closure and clinical heart failure or the presence of rales in this series of patients. There was a significant correlation between the presence of abnormal mitral valve closure and a third sound gallop (P <0.05).

Echocardiographic Measurements and Mortality

Results of the analysis of variables showing which echocardiographic findings might predict mortality are presented in Table II.

First echocardiogram: Although an echocardiographically dilated left ventricle and abnormal mitral valve closure were more common on admission among those who subsequently died, neither finding alone was useful in predicting mortality. Only when these two abnormalities were combined were they of significant value in predicting death (Fig. 7A). The mortality rate for the group in which both measurements could be made was 20 percent (9 of 46). The mortality rate among those in whom both variables were abnormal was 55 percent (6 of 11), whereas only 9 percent (3 of 35) of patients without this combination died. This difference was significant (P <0.001). The $LVID_d$ index/PR-AC ratio was also useful in predicting mortality (P <0.005) at the time of admission (Fig. 7B). The presence of abnormal wall motion was not useful for this purpose.

Last echocardiogram in the coronary care unit: Results of analyzing the same variables using each patient's last echocardiogram obtained in the

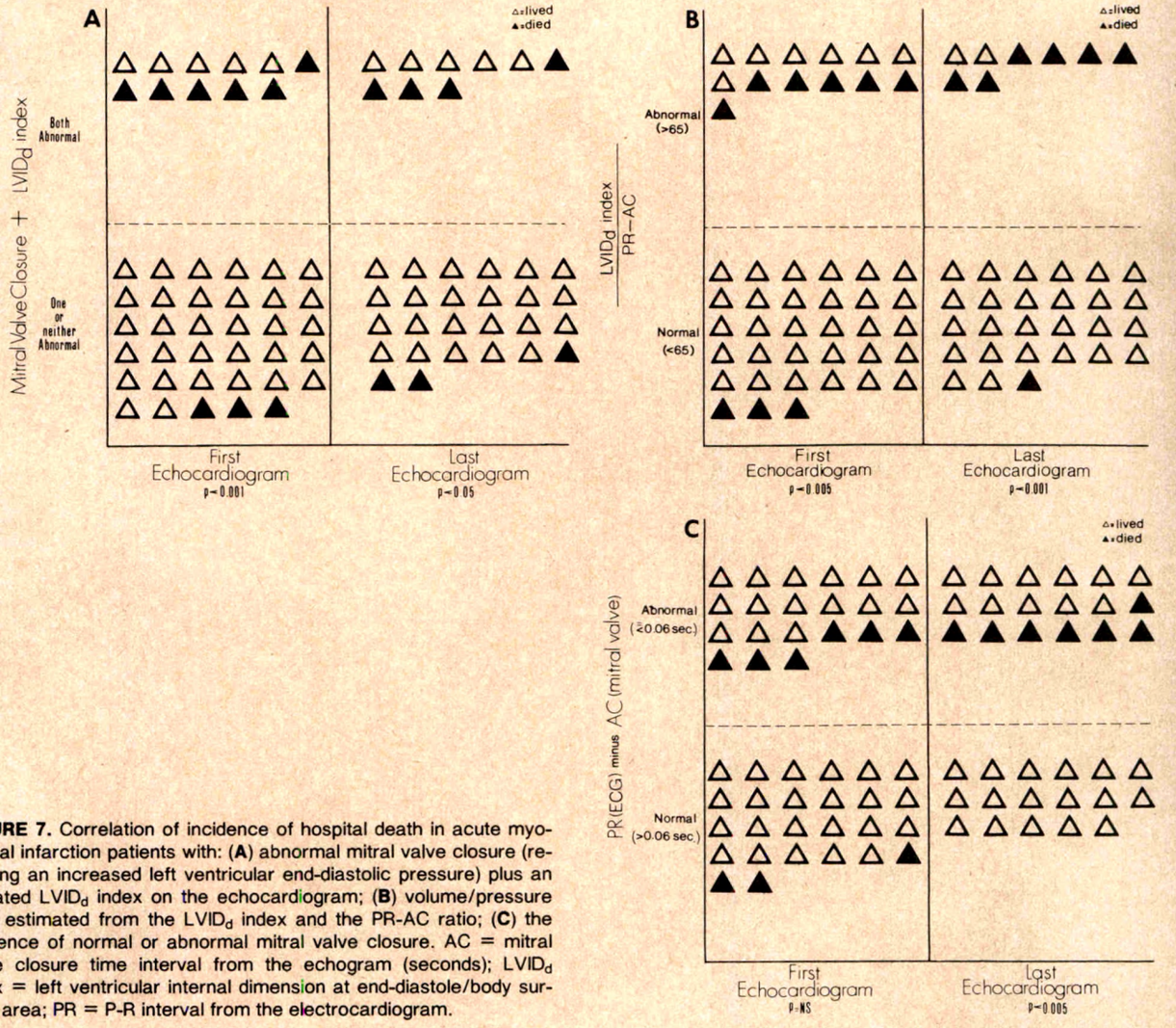

FIGURE 7. Correlation of incidence of hospital death in acute myocardial infarction patients with: (**A**) abnormal mitral valve closure (reflecting an increased left ventricular end-diastolic pressure) plus an elevated $LVID_d$ index on the echocardiogram; (**B**) volume/pressure ratio estimated from the $LVID_d$ index and the PR-AC ratio; (**C**) the presence of normal or abnormal mitral valve closure. AC = mitral valve closure time interval from the echogram (seconds); $LVID_d$ index = left ventricular internal dimension at end-diastole/body surface area; PR = P-R interval from the electrocardiogram.

coronary care unit were different. Patients who had only one echocardiogram were excluded from this analysis. When these later echocardiograms were used, the presence of abnormal mitral valve closure alone was significant (P <0.005) in predicting mortality (Fig. 7C). Most significant at this time was the $LVID_d$ index/PR-AC ratio (P <0.0001) (Fig. 7B). Only 1 of 27 patients who had a volume/pressure ratio of less than 65 on his last echocardiogram died in the hospital, whereas 6 of 8 patients with values greater than 65 died before hospital discharge. Figure 8 shows the ratios for individual patients and indicates whether or not they died in the hospital. A value of 65 seemed to provide the separation of survivors and nonsurvivors. Abnormal wall motion was still not helpful in predicting mortality.

Clinical Findings and Mortality

Results of the analysis of clinical variables in predicting mortality are presented in Table III. There was significantly increased mortality in patients more than 60 years of age (P <0.025) and in those with a third sound gallop (P <0.05), rales (P <0.05) or clinical heart failure (Killip classification) on admission (P <0.05). Forty-eight hours after admission a third sound gallop was a better predictor of mortality (P <0.001) than either rales (P <0.01) or clinical heart failure on the basis of the Killip classification (P <0.01). Mortality was significantly different between patients in Killip class I (no heart failure) and those with class II heart failure (third sound gallop or bilateral rales, or both, without overt pulmonary edema or shock) at 48 hours (P <0.01) but not on admission.

Sequential changes: Although some daily changes in both the left ventricular internal diameter at end-diastole ($LVID_d$) index and the P-R minus mitral valve closure (PR-AC) interval were observed, the most striking sequential changes related to mortality were in the $LVID_d$ index/PR-AC ratio as illustrated in Figure 9. For clarity, lines indicating change were drawn only for patients whose values went from the area of high mortality to that of low mortality or vice versa. The figure shows that abnormal echocardiographic findings preceded death by many hours or even days and were not due to sudden terminal events. There were three nonsurvivors with a "nor-

TABLE III

Analysis of Clinical Findings in Predicting Mortality in Acute Myocardial Infarction

	Patients (no.)	Lived (no.)	Died (no.)	*P* Value
Complete clinical profile obtained	64	49	15	
Location of infarction				
Anterior wall	28	19	9	NS
Inferior wall	33	28	5	
Both	3	2	1	
Age (yr)				
<60	29	26	3	<0.025
≥60	35	23	12	
Sex				
Male	36	28	8	NS
Female	28	21	7	
SGOT				
≤250 units	35	29	6	NS
>250 units	29	20	9	
On admission				
Killip class				
I	27	24	3	NS
II	31	22	9	<0.05
III	4	2	2	
IV	2	1	1	
S_3 gallop present	20	12	8	<0.05
Bilateral rales present	36	24	12	<0.05
At 48 hours				
Killip class				
I	21	21	0	<0.01
II	39	28	11	
III	0			
IV	0			
S_3 gallop present	15	7	8	<0.001
Bilateral rales present	39	28	11	<0.01

Killip class: I = no heart failure; II = third sound gallop or bilateral rales, or both; III = pulmonary edema; IV = shock; SGOT = serum glutamic oxaloacetic transaminase; S_3 = third heart sound.

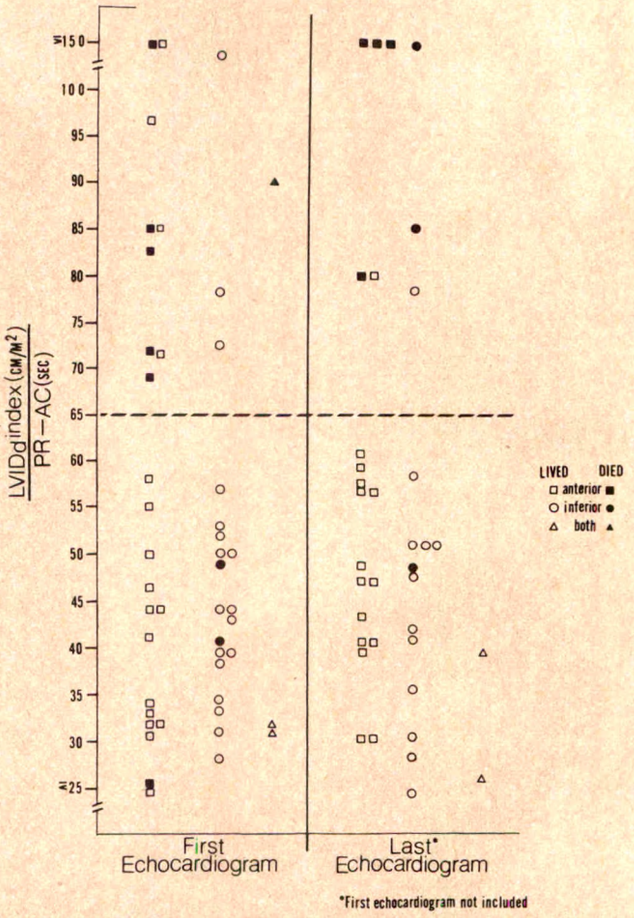

FIGURE 8. Individual values for the echocardiographic volume/pressure ratio in patients with acute myocardial infarction. Sixty-five is the value that best separates the survivors from the nonsurvivors. Abbreviations as in Figure 7.

mal volume/pressure ratio" in the admission echocardiogram whose ratio became abnormal before death and six of seven survivors with an abnormal ratio on admission whose ratio became normal while they were in the coronary care unit.

Discussion

Technical feasibility: This study demonstrates that technically adequate bedside echocardiograms can be obtained routinely in patients with acute myocardial infarction. Information about left ventricular wall motion and size was obtained on 59 of 64 patients (92 percent). Although mitral valve echoes were recorded on 61 of 64 cases (95 percent), a P-R minus mitral valve closure interval could be measured in only 47 of 61 patients (77 percent) because of atrial fibrillation, heart block and sinus tachycardia in some patients and difficulty in accurately measuring the onset of the electrocardiographic P wave in others. With sinus tachycardia, the left ventricular filling period is often so short that the E and A points on the mitral valve echogram cannot be distinguished.

Left ventricular wall motion: Echocardiography was a sensitive indicator in the early detection of abnormal areas of wall motion corresponding to the electrocardiographic site of transmural infarction in this study, but it is not possible to make a diagnosis of myocardial infarction from the echocardiogram. Abnormal motion is seen with chronic coronary artery disease without evidence of infarction,[1,2] and it may be seen transiently during stress in patients who have normal echocardiographic motion at rest.[1,15] We have observed the same changes in patients with a diagnosis of preinfarction angina. The echocardiographic changes may be useful in determining whether symptoms are cardiac in origin when infarction has not taken place or before diagnostic electrocardiographic changes are present. Other conditions, including cardiomyopathy,[16] left bundle branch block,[17,18] right ventricular volume overload,[19,20] left ventricular volume overload[21] and prosthetic valve

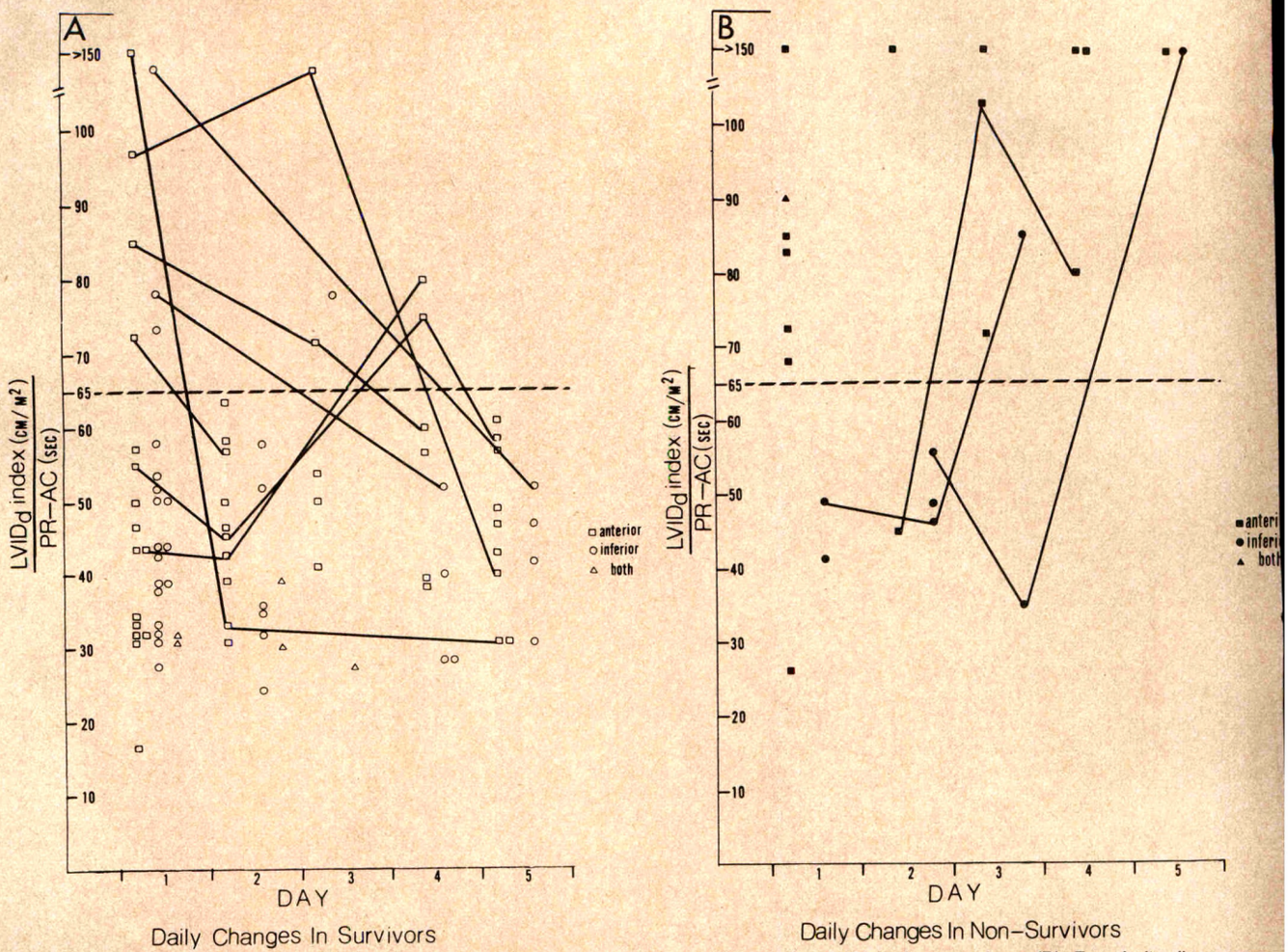

FIGURE 9. Sequential changes in the echocardiographic volume/pressure ratio in survivors (**A**) and nonsurvivors (**B**). For clarity, lines were only drawn for patients who change from areas of high mortality to low mortality, or vice versa. Abbreviations as in Figure 7.

surgery,[22] affect echocardiographic motion and must also be considered.

Left ventricular internal dimension: Because the left ventricle may be asymmetrical in coronary artery disease, especially during contraction, caution must be exercised in using echocardiographic left ventricular dimensions to estimate volumes. Studies comparing volumes derived from biplane angiograms with those derived from single echocardiographic dimensions in patients with coronary artery disease support the use of a single left ventricular diastolic dimension for estimating diastolic volume.[5] Although we found significant correlation between an increased left ventricular internal dimension and congestive heart failure, some patients with heart failure had a normal index (Fig. 6). Other investigators have also found a normal value for this dimension in patients with clinical signs of heart failure.[23,24]

Mitral valve closure: In a series of patients in whom the P-R minus mitral valve closure (PR-AC) interval was correlated with left ventricular pressure, it was found that when mitral valve closure was prolonged enough to reduce the PR-AC interval to 0.06 second or less the left ventricular end-diastolic pressure was 20 mm Hg or greater with an "atrial kick" of at least 8 mm Hg.[12] It is not certain that the correlation between valve motion and pressure demonstrated in patients with chronic disease is as reliable in patients with acute myocardial infarction and a wide range of P-R intervals.

We do not know how often decreased compliance was responsible for abnormal mitral valve closure. Presumably this was true in the patients with a left ventricle of normal size. There was no significant correlation between abnormal mitral valve closure and either increased left ventricular size or clinical heart failure based on the presence of rales or a third sound gallop, or both. However, abnormal mitral valve closure did correlate significantly with the presence of a third sound gallop. It is possible that increased left ventricular size with heart failure was also responsible for increased pressures in many cases.

Predicting mortality: Pulmonary arterial pressure, capillary wedge pressure and cardiac output have been useful in predicting mortality in patients with acute infarction.[25–27] Diamond and Forrester,[28]

using left heart catheterization, have shown a high correlation between left ventricular compliance and prognosis in such patients. Investigation of left ventricular pressure-volume relation in these patients has been limited by the lack of an acceptable means of measuring left ventricular volume in acutely ill persons. Recently Smith et al.[24] studied the volume-pressure relation ("compliance") in 14 patients with acute myocardial infarction. They used the pulmonary arterial end-diastolic pressure as the left ventricular filling pressure and echocardiographic dimensions to determine left ventricular volumes. The sequential compliance values were more useful than either left ventricular filling pressure or left ventricular volume in predicting survival in that study.

We do not know how well our echocardiographic volume/pressure ratio represents compliance but our results show that it may be useful in predicting mortality and in following a patient's clinical course. It is also unknown whether the combined presence of abnormal mitral valve closure and an increased left ventricular internal dimension at end-diastole on admission, which was highly significant in predicting mortality, represents predominantly decreased compliance or heart failure.

Clinical implications: This study does not prove that the echocardiogram accurately reflects left ventricular volume and end-diastolic pressure. These assumptions are based on previous studies in patients with chronic disease. This study does demonstrate: (1) technically adequate echocardiograms can be obtained in most patients with acute infarction. (2) Echocardiography is a sensitive method of detecting abnormalities of left ventricular wall motion corresponding to the electrocardiographic site of infarction. (3) An echocardiographically dilated left ventricle usually indicates congestive heart failure. (4) Echocardiographic measurements and their relation to each other are useful in determining prognosis in individual patients.

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Echocardiography in Aortic Root Dissection and Dilatation

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Six patients with aortic root dissection proved by angiography, surgery or autopsy, and six patients with aortic root dilatation were studied by echocardiography. Echocardiography was diagnostic in five of six patients with dissection and suggestive in the sixth, disclosing anterior and posterior dissection in three, anterior dissection in one and posterior dissection in one. The recording of a double echo in the aorta was the diagnostic feature. Angiography was diagnostic in four of the six patients, yielded a false negative result in one and was not performed in one. Six patients with dilatation had an enlarged aortic root by echocardiography. Left ventricular size, stroke volume, ejection fraction, aortic regurgitant flow and velocity of circumferential fiber shortening were calculated in 11 patients. Echocardiography was extremely helpful in the diagnosis, management and follow-up in patients with aortic dissection or dilatation.

Echocardiography is a noninvasive harmless bedside diagnostic technique. It is therefore especially helpful in the management of acutely ill patients and in following up those needing repeated examinations. This study reports the echocardiographic findings in 12 patients with aortic root dissection or dilatation and the associated abnormalities of aortic insufficiency, hemopericardium or abnormal ventricular function.

Material and Methods

Twelve patients, six with aortic root dissection and six with aortic root dilatation, were studied by echocardiography using a Unirad echocardiograph with a 2.5 megacycle transducer. The transducer was located in the usual position along the left sternal border and angulated to give four views: (1) the aortic root, (2) roll-off from aortic root to mitral valve, (3) the mitral valve, and (4) the left ventricular internal dimension. The study was recorded on Polaroid® prints or a strip chart recorder. The echocardiograms were evaluated by (1) examination of the echo patterns, and (2) measurements and calculations. Left ventricular volumes were calculated by the formula EDV = 59 (LVD) − 153 and ESV = 47 (LVS) − 120,[1] where EDV = end-diastolic volume, LVD = left ventricular diastolic diameter, ESV = end-systolic volume and LVS = left ventricular systolic diameter. Aortic regurgitant flow was calculated by the formula QAr = QAt − QM,[2,3] where QAr = aortic regurgitant flow, QAt = aortic valve total flow and QM = mitral valve flow. Velocity of circumferential fiber shortening was calculated by the formula (LVD-LVS)/dt/LVD,[4] where dt = duration of minor axis shortening.

Dissection was confirmed by autopsy (two cases). Angiograms were obtained in five patients at the time of the echocardiogram; in one (Case 5) an angiogram 3 months prior to the echocardiogram showed a normal ascending aorta. Three patients with dilatation had angiograms showing dilatation and aortic insufficiency. The clinical and echocardiographic data are summarized in Tables I and II.

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Results

Aortic dissection: We found that a double echo recorded from the anterior or posterior aortic root was diagnostic of aortic dissection. Three patients had double echoes both anteriorly and posteriorly suggesting circumferential dissection, which was found at surgery or autopsy (Fig. 1 to 3). In one patient with a mid-aortic echo extending through systole, an anterior dissection was diagnosed angiographically and confirmed at surgery (Case 3). One patient had a posterior double echo and a posterior intimal flap by angiogram (Fig. 4). One patient with

TABLE I

Aortic Root Abnormalities

Case no.	Cause	Surgery or Autopsy	AI	Angiogram	Double Echo	Aortic Root Diameter (cm)	FI, AML	LVE
			Aortic Root Dissection					
1	Atherosclerosis	Both	1+	Positive	A,P	...	+	−
2	Cystic medial necrosis	Autopsy	4+	Negative	A,P	...	+	−
3	Marfan's syndrome	Surgery	3+	Positive	A	...	+	+
4	Unknown	Neither	0	Positive	P	...	−	−
5	Marfan's syndrome	Surgery	0	Negative*	A,P	...	−	−
6	Aortic stenosis and hypertension	Neither	0	Positive	*	...	−	−
			Aortic Root Dilatation					
7	Marfan's syndrome	Autopsy	3+	Dilated	...	6.2	−	+
8	Cystic medial necrosis	Surgery	2+	Dilated	...	5.3	+	−
9	Congenital	Neither	2+	...	...	5.0	−	−
10	Marfan's syndrome	Neither	0	...	...	4.4	−	−
11	Cystic medial necrosis	Surgery	4+	Dilated	...	4.5	+	+
12	Syphilis	Neither	2+	Dilated	...	4.6	−	+

* See text.

+ = present; − = absent.

A = anterior; AI = clinical aortic insufficiency; AML = anterior mitral leaflet; FI = flutter; LVE = left ventricular enlargement; P = posterior.

TABLE II

Echocardiographic Measurements and Calculations

Case no.	Aortic Root Diameter (cm)	LVD	LVS	EDV	ESV	SV ($\dot{Q}$At)	EF	AML Closure Rate	$\dot{Q}$M	$\dot{Q}$AR	V_{CF}	AI
					Aortic Root Dissection							
1	4.5	...	...	...	...	...	...	0.40	43	...	...	1+
2	4.2	5.0	3.3	142	38	104	0.73	0.76	62	42	1.14	4+
3	4.5	6.0	4.8	199	105	94	0.47	0.60	32	62	0.47	3+
4	4.7	4.8	3.8	127	58	69	0.54	0.76	55	14	0.84	0
5	4.6	3.4	2.9	47	20	27	0.57	0.50	20	−7	0.97	0
6	5.0	5.5	4.6	172	96	76	0.44	1.80	52	24	0.55	0
					Aortic Root Dilatation							
7	6.2	9.5	7.8	437	248	189	0.43	1.80	15	174	0.71	3+
8	5.3	5.9	3.0	197	21	176	0.89	1.04	45	131	1.20	2+
9	5.0	5.2	3.8	157	60	97	0.62	0.64	19	78	1.08	2+
10	4.4	4.4	3.1	107	25	82	0.77	0.84	63	19	1.05	0
11	4.5	7.1	5.1	267	120	147	0.55	1.66	48	99	1.13	4+
12	4.6	7.8	7.0	307	209	98	0.32	0.96	35	63	0.51	2+

AI = clinical aortic insufficiency (grade 0 to 4+); AML closure rate = closure rate of anterior leaflet of mitral valve (cm/sec); EDV = end-diastolic volume (cc); EF = ejection fraction; ESV = end-systolic volume (cc); LVD = left ventricular diastolic diameter (cm); LVS = left ventricular systolic diameter (cm); $\dot{Q}$AR = aortic regurgitant flow (cc); $\dot{Q}$AT = aortic valve total flow (cc); $\dot{Q}$M = mitral valve flow (cc); SV = stroke volume (cc); V_{CF} = velocity of circumferential fiber shortening (cm/sec).

aortic root dissection had an abnormal echo pattern with multiple echoes from the aorta suggesting thickening of the aortic wall and dilatation (Case 6). Dissection was not interpreted prospectively from this patient's echocardiogram because of the absence of a double echo, but it was confirmed by angiography 2 weeks later. A subsequent echocardiogram was diagnostic of pericardial effusion (hemopericardium found on pericardiocentesis). A later follow-up echocardiogram indicated healing with thickened aortic walls, confirmed by angiography. It is now clear that a thickened aortic wall is compatible with, but not diagnostic of dissection. Thickening was seen in acute dissection (Case 3), healed dissection (Case 6) and dilatation without dissection (Case 7).

Aortic dilatation: All six patients with dilatation had an enlarged aortic root diameter ranging from 4.4 to 6.2 cm (normal 3.1 to 3.9)[5] measured between the outer margins of the anterior and posterior aortic walls.

Aortic insufficiency: Five of the 12 patients had fluttering of the anterior leaflet of the mitral valve, and all 5 had aortic insufficiency. Three patients with aortic insufficiency did not have such fluttering. There was no correlation between the severity of the insufficiency and leaflet flutter.

Table II lists the measurements and calculations made in these patients. Patients with aortic insufficiency had an increased stroke volume and aortic regurgitant flow, but there was no correlation between aortic insufficiency and ejection fraction, closure rate of the anterior mitral leaflet or velocity of circumferential fiber shortening.

Discussion

Dissecting hematomas occur most frequently in the ascending aorta. More than half of the intimal tears are located within 2 cm of the aortic valve, and mortality is greatest when the tear is in this area.[6,7] There is a 3 percent incidence rate of sudden death in dissecting hematoma and an 83 percent mortality rate in 1 month if the lesion is untreated.[6] The disease can be rapidly progressive, and up to 66 percent of these hematomas may rupture into the pericardial sac.[7] Furthermore, the dissection may extend weeks to months after its onset. A diagnostic tool that can examine the aortic root repeatedly at the bedside without risk to the patient is therefore highly desirable. Echocardiography of the aortic root fulfills these criteria and we found it to be extremely helpful in the diagnosis and management of patients with aortic root abnormalities.

Echocardiography can display the following in an examination of the aortic root: (1) root diameter, (2) presence of one or more discrete walls anteriorly or posteriorly, (3) width of the aortic wall, (4) the aortic cusps. In addition, the echocardiogram visualizes changes in the anterior mitral leaflet secondary to aortic insufficiency, may demonstrate pericardial effusion and permit hemodynamic measurements to be performed to evaluate cardiac function. Our results indicate that (1) a double echo recorded from

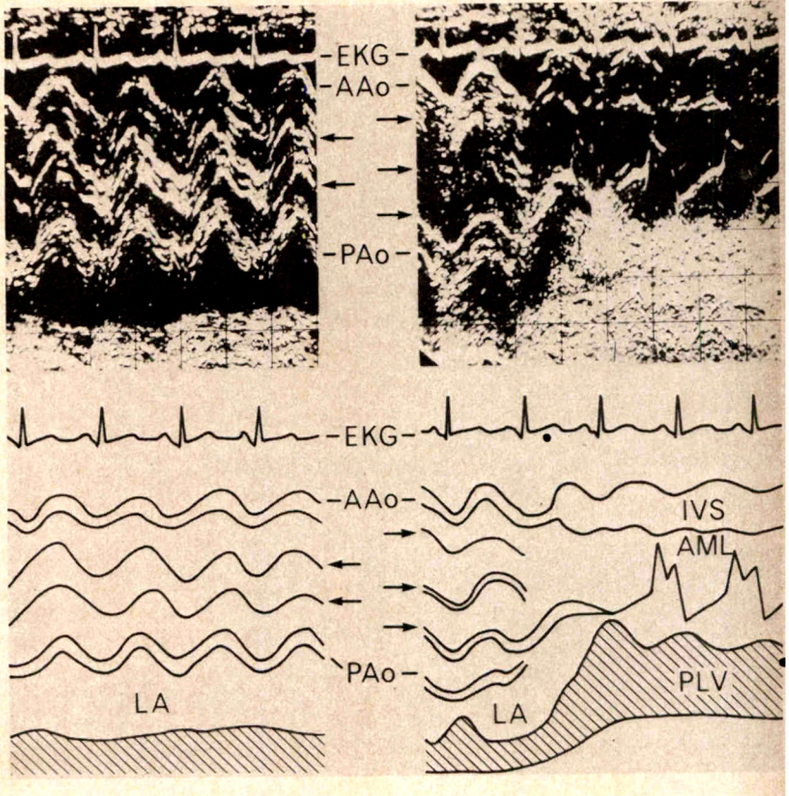

FIGURE 1. Case 1. Aortic dissection. Echocardiogram demonstrates multiple parallel discrete echoes in the aorta **(arrows).** The posterior aortic wall (PAo) is displaced posteriorly into the left atrium (LA) on the roll-off view of the aorta to the anterior leaflet of the mitral valve (AML) and is not contiguous with this leaflet. AAO = anterior aortic wall; EKG = electrocardiogram; IVS = interventricular septum; PLV = posterior left ventricular wall.

the aortic root indicates aortic dissection; (2) the diameter of the aortic root is accurately determined by echocardiography; and (3) patients with aortic insufficiency will have increased stroke volume and aortic regurgitant flow as calculated from the echocardiogram.

Validation of method and clinical implications: The validity of demonstrating the aortic root and the aortic cusps by echocardiography was shown in 1968.[8] Several investigators[9–11] have used A and B mode scanning to reveal thoracic aneurysms. Measurements obtained from suprasternal echocardiography using both A and M modes showed excellent correlation between dimensions found on echocardiography and angiography.[12] There are two reports of studies using the conventional left sternal border view of the aortic root. Millward et al.[13] reported a case of dissecting hematoma rupturing into the right atrium. The aortic root showed anterior and posterior double echoes, as seen in three of our cases. Nanda et al.[5] reported six cases of aortic root dissection. They postulated three echocardiographic findings allowing de-

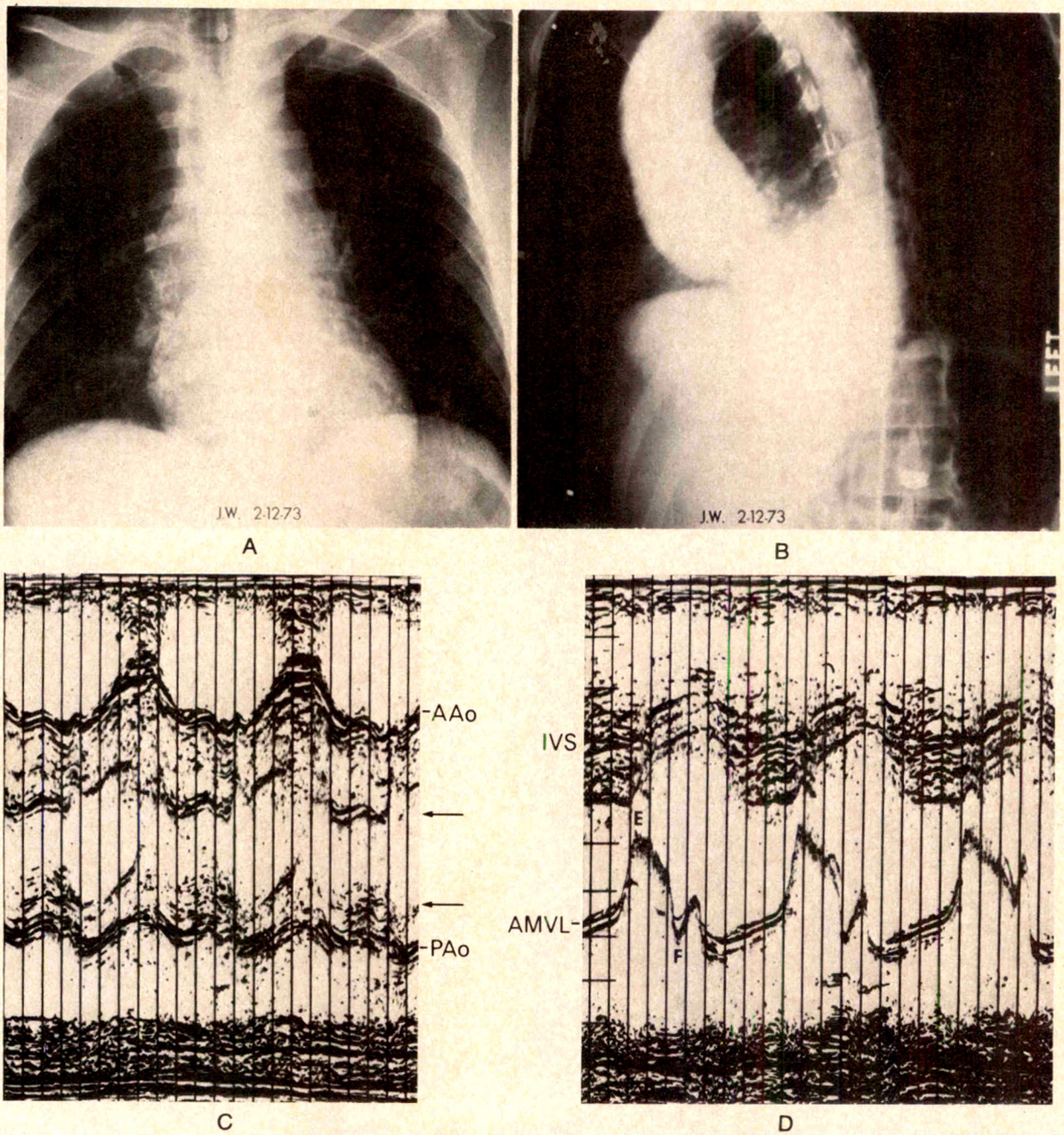

FIGURE 2. Case 2. Aortic dissection. **A,** chest film shows prominent ascending aorta. **B,** aortic angiogram shows dilated aortic root, aortic insufficiency and no evidence of dissection. **C,** echocardiogram shows a double echo both anteriorly and posteriorly **(arrows)** and reveals an enlarged aortic root (6.2 cm). **D,** echocardiogram shows flutter of the descent slope (E-F) of the anterior mitral valve leaflet (AMVL), indicating aortic insufficiency. Abbreviations as in Figure 1.

finitive diagnosis of dissection: (1) enlargement of the aortic root, (2) widening of the anterior wall or separation of the posterior wall, and (3) maintenance of parallelism between the separated walls.

Enlargement of the aortic root was seen in all six of our patients with dilatation without dissection; widening of the aortic wall was seen in four of the six. Although parallelism of the double echoes was usually seen, it was not complete (Fig. 4). We found that only multiple discrete or double echoes arising from the anterior or posterior aortic wall, or both, are diagnostic of dissection, particularly when the double echoes are not continuous with the septum anteriorly or the mitral leaflet posteriorly (Fig. 1, 3 and 4). Double echoes may be seen in calcific aortic stenosis; however, they are usually less discrete, and normal aortic leaflets are not seen. When dissection is present, normal leaflets may be seen (Fig. 3), thus differentiating dissection from calcific aortic stenosis. We suggest that all patients suspected of having a dissecting hematoma have echocardiograms in addition to angiograms. With the increased risk of angiography (mortality 1.7 percent)[14] in this disease, echocardiography would be preferable for repeat evaluation of these patients.

Anterior mitral leaflet echoes in aortic regurgitation: As reported previously,[15] flutter of the anterior leaflet of the mitral valve was diagnostic of aortic insufficiency (Fig. 2D). However, not all patients with aortic insufficiency had flutter of the anterior mitral leaflet. Other findings reported in aortic insufficiency are an increased descent slope, premature closure and delayed opening of the anterior mitral leaflet. We found no correlation between descent slope and aortic insufficiency (Table II), and one patient (Case 9) had premature closure and one (Case

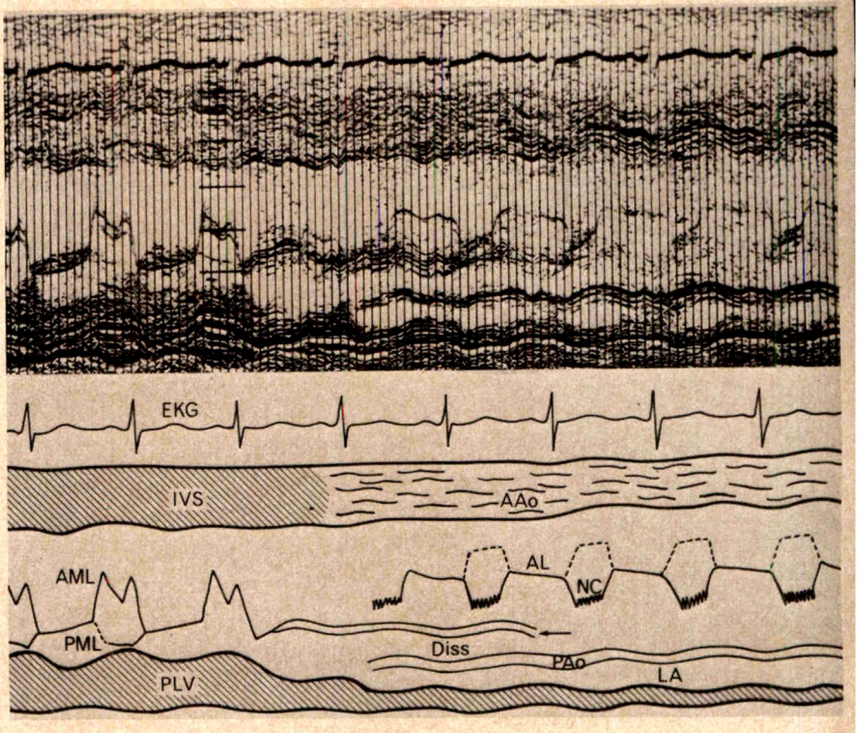

FIGURE 3. Case 3. Aortic dissection. Echocardiogram on admission. Strip chart record with roll-off from anterior mitral valve leaflet to aorta. The anterior aortic wall (AAo) is markedly thickened. The posterior aortic wall (PAo) is displaced into the left atrium (LA) with a discrete double echo not contiguous with the anterior mitral leaflet. The patient had circumferential dissection at surgery. AL = aortic leaflets; Diss = dissection; NC = noncoronary cusp; PML = posterior mitral leaflet; other abbreviations as in Figure 1.

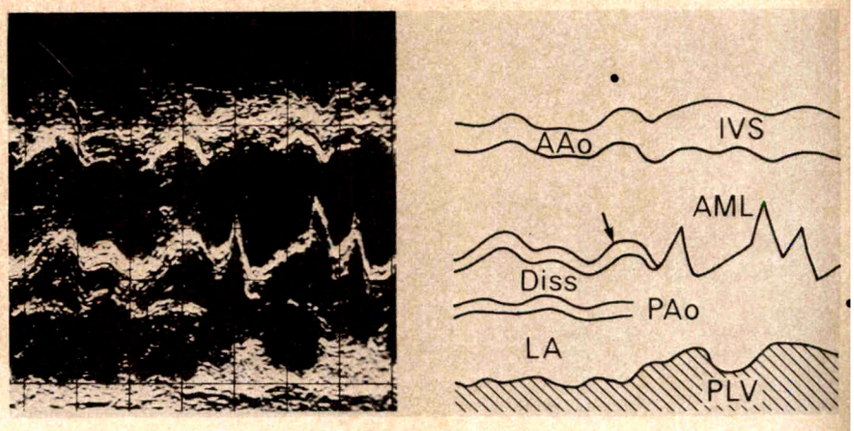

FIGURE 4. Case 5. Aortic dissection. Echocardiogram with roll-off from aorta to anterior mitral leaflet (AML). There is a double echo posteriorly demonstrating dissection, and the posterior aortic wall (PAo) is displaced into the left atrium and is not contiguous with the anterior mitral leaflet. Abbreviations as in Figures 1 and 3.

10) had delayed opening. We did find a correlation between aortic insufficiency and aortic regurgitant flow (Table II), although the degree of clinical or angiographic aortic insufficiency did not correlate with the magnitude of regurgitant flow.

In conclusion, echocardiography was diagnostic of aortic root dissection in five of six patients and suggestive in one and thus had a diagnostic accuracy equal to that of angiography. Echocardiography was diagnostic in the six patients with aortic root dilatation. It proved to be of great value in following up both groups of patients serially and in managing the associated conditions of aortic insufficiency, hemopericardium and cardiac enlargement.

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Echocardiographic Criteria for Aortic Root Dissection

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Echocardiographic findings from 10 patients without clinical indications of aortic root dissection or aortic valve disease and from 1 patient with angiographic confirmation of aortic root dissection are reported and compared. Previously reported echocardiographic findings were confirmed in the patient with aortic root dissection. These include (1) a widened posterior or anterior aortic wall, or both; (2) parallel motion of the separated margins of the aortic root walls; and (3) aortic root dilatation (42 mm or more at end-systole). However, all three findings were also noted in 5 of the 10 patients without clinical indications of aortic root dissection or aortic valve disease, and at least two of the three findings were noted in the remaining 5 patients. Echocardiographic detection of aortic root dissection appears to be most reliable when clinical indications of the anomaly are present.

Echocardiography has proved useful in detecting aortic aneurysms involving the aortic root in patients with clinical indications of this potentially lethal disease.[1–3] However, the echocardiographic pattern of aortic root dissection may be seen in patients without clinical evidence of dissection. This consideration illustrates the need for caution in diagnosing this anomaly by ultrasound unless the clinical course of the patient is consistent with this disorder.

Methods

A clinical description of the patients in this study is found in Table I.

The ultrasonic examinations were conducted utilizing either a Smith-Kline Ekoline 20 or a Picker Echoview 10 ultrasonoscope. The transducer used in all studies was an Aerotech 1.27 cm, 2.25 megacycle, 5 cm focused transducer. Continuous recordings were made on an Electronics for Medicine or Honeywell 1856 strip chart recorder.

All measurements were made by the same technique previously reported in evaluation of patients with aortic root dissection.[1] Aortic root width was measured from the most anterior echo of the anterior aortic wall to the most posterior echo of the posterior aortic wall during systole. Wall thickness was measured from the outer limit of each wall to the inner limit of the lesser components during systole (Fig. 1).

Results

Aortic root dissection: The single patient with dissection (Table II, Case 11) had aortic root dilatation (70 mm), increased posterior aortic wall thickness (15 mm) and maintenance of parallel motion between the separated margins of the aortic walls as described by Nanda et al.[1] Motion of the aortic cusps was normal. The intensity of the echoes from the outer portion of the thickened wall was greater than those from the inner portion, with the space between the inner and outer limits of the thickened wall being filled with nondescript echoes. Changes in transducer angle produced variations in aortic root and aortic wall width.

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Patients without dissection: Six of the 10 patients without clinical indications of aortic root dissection (Table II) had aortic root enlargement (42 mm or more at end-systole[1]). Aortic root width ranged from 37 to 47 mm at end-systole. Marked thickening (10 mm or more)[1] of the posterior aortic wall at end-systole occurred in 9 of the 10 patients without dissection. Posterior aortic wall thickness at end-systole ranged from 8 to 11 mm. No patient had a thickened anterior aortic wall at end-systole, as previously defined in aortic root dissection (16 mm or more[1]) although in three this structure was consider-

TABLE I

Clinical Findings

Case no.	Age (yr) & Sex	Primary Clinical Complaint	Clinical Diagnosis	Invasive Confirmation	Comment
			A. Normal Patients		
1	24M	None	Normal member of family with history of IHSS	None	No auscultatory abnormalities
2	71M	Fatigue, chest pain	CHF	None	S_3, LSB sys M, ECG ischemia
3	63F	Fatigue	MS	None	Diastolic rumble?, opening snap vs. S_3
4	66M	Fatigue, chest pain	CHF	Cath, angio	3–4+ MR
5	38M	Fatigue	Alcoholic myopathy	None	S_3, S_4, no murmurs
6	43F	Fatigue	CHF	None	No murmurs, S_3
7	24F	Fatigue	MS, MR, AR	Cath	Trivial AR, mild MS, mild MR (rheumatic)
8	58M	Hernia	Right inguinal hernia	None	II/IV SEM
9	32M	Fatigue with exercise	ASD	Cath	Secundum ASD (2.5/1)
10	42M	Drug addiction	Hypertension, LVF, drug addiction	None	SEM, S_4
			B. Aortic Root Dissection		
11	56M	Fatigue, back pain	AR	Cath, angio	Rapid onset AR, at angio 4+ AR

Angio = angiography; AR = aortic regurgitation; ASD = atrial septal defect; Cath = cardiac catheterization; CHF = congestive heart failure; ECG = electrocardiogram; IHSS = idiopathic hypertrophic subaortic stenosis; LSB = left sternal border; LVF = left ventricular failure; MR = mitral regurgitation; MS = mitral stenosis; SEM = systolic ejection murmur; S_3 = third heart sound; S_4 = fourth heart sound; Sys M = systolic murmur.

TABLE II

Echocardiographic Findings*

Case no.	Aortic Root Dimensions (mm)		
	Width	Wall Thickness	
		Anterior	Posterior
	A. Normal Patients		
1	37	5	10
2	42	10	10
3	45	3	10
4	37	9	10
5	39	12	11
6	43	10	8
7	43	4	10
8	47	5	11
9	39	9	11
10	43	7	13
	B. Aortic Root Dissection		
11	70	4	15

*The echocardiogram revealed normal valve cusps in all cases.

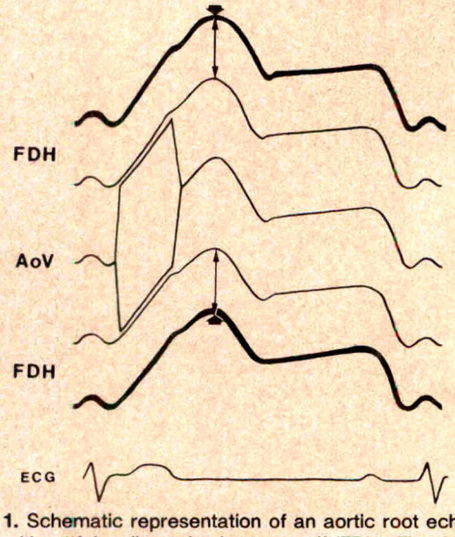

FIGURE 1. Schematic representation of an aortic root echogram in a patient with a "false dissecting hematoma" (FDH). The **thin arrows** indicate the thickness of the false hematoma, the **thick arrows** the width of the aortic root image measured at end-systole. AoV = aortic valve; ECG = electrocardiogram.

ably widened (10 mm or more[4]). Anterior aortic wall thickness at end-systole ranged from 3 to 12 mm. In all 10 patients parallelism was maintained between the inner and outer limits of the thickened wall throughout the cardiac cycle (Fig. 2). The outer portion of the thickened wall was more intense than the inner portion in all cases (Fig. 2). The space between the outer and inner limits of the thickened wall was echo-free in two cases. In the remaining eight patients this space was filled with nondescript echoes. The appearance of the aortic valve cusps was normal in all patients, as previously reported,[4] with their motion extending to the periphery of the inner lumen in systole (Fig. 2). Motion of at least one valve cusp was defined in all patients.

Changes in transducer angle also produced variations in aortic wall thickness in all 10 patients without clinical indication of aortic root dissection (Fig. 3). These changes ranged from 3 to 6 mm, with the thickness usually decreasing as the transducer was directed more superiorly and medially toward the ascending aorta. The width of the aortic root image also changed, but in more random fashion. These changes ranged from 5 to 11 mm. The more basal angulation of the transducer yielded a wider aortic root dimension in 6 of the 10 patients; in the remaining 4 patients the more basal angle produced little appreciable change in aortic root dimension.

Discussion

Recently, Nanda et al.[1] described several echocardiographic criteria for aortic root dissection including (1) enlargement of the aortic root (42 mm or more); (2) marked thickening (16 to 21 mm) of the anterior wall of the aorta at the root level or a wide separation of the posterior aortic wall (10 to 13 mm), or both; and (3) maintenance of parallelism between the separated margins of the walls. Normal motion of the aortic valve cusps was also noted in most patients with aortic root dissection.

The findings in our one patient with aortic root dissection confirm the echocardiographic criteria for

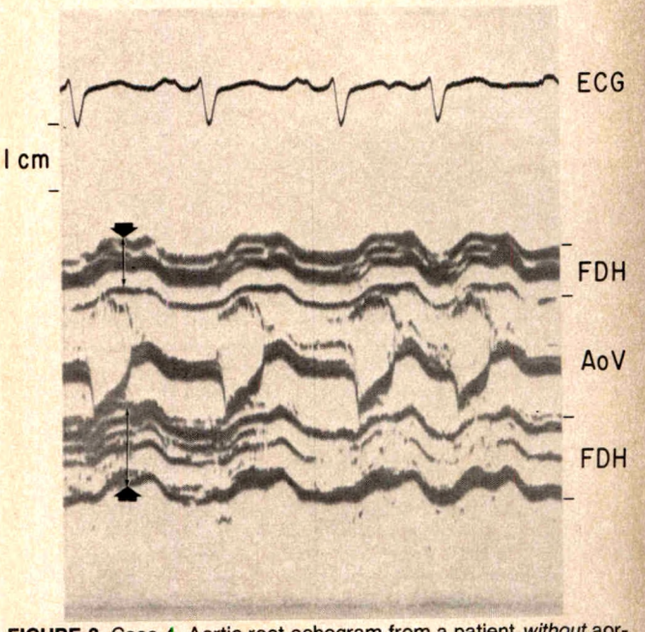

FIGURE 2. Case 4. Aortic root echogram from a patient *without* aortic root dissection illustrates two of the three previously reported criteria for this lesion. There is a parallel widening of the posterior aortic wall (10 mm or more), and the aortic valve cusps (AoV) move only to the inner border of the wall. The aortic root is not enlarged. There is also parallel thickening of the anterior aortic wall (8 mm) although this thickness is not as great as that reported in aortic root dissection. FDH = false dissecting hematoma; ECG = electrocardiogram.

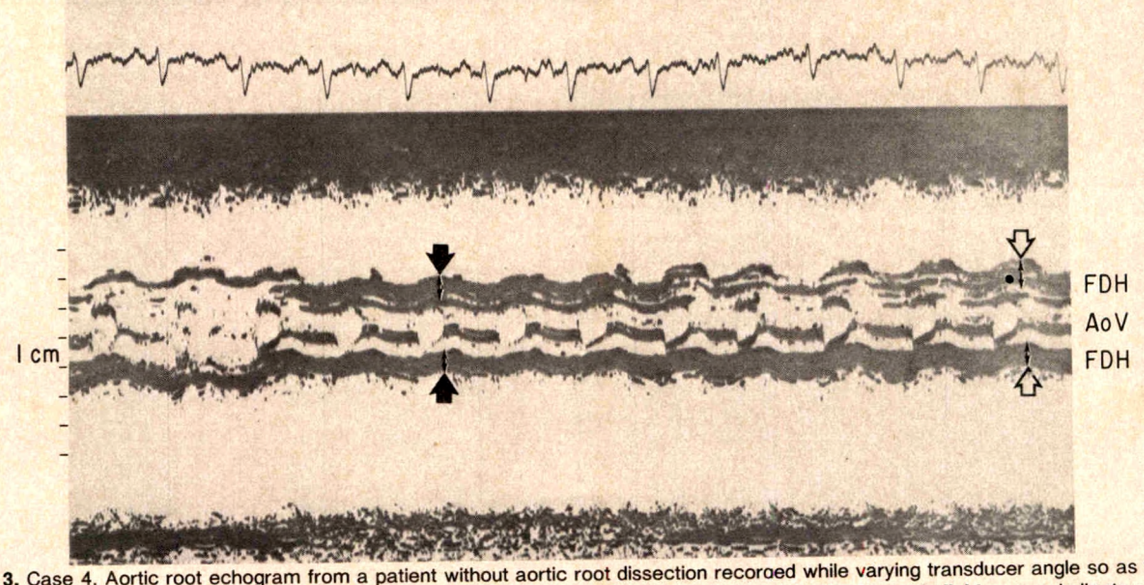

FIGURE 3. Case 4. Aortic root echogram from a patient without aortic root dissection recorded while varying transducer angle so as to sweep the aortic area. The **wide dark arrows** indicate aortic root width with the beam pointed more inferiorly. The **wide light arrows** indicate aortic root width with the beam rocked slowly in a superior and medial manner toward the ascending aorta. The **thin double-headed arrows** indicate aortic wall thickness. Note the variability in aortic root width and aortic wall thickness previously reported as consistent with a localized hematoma.

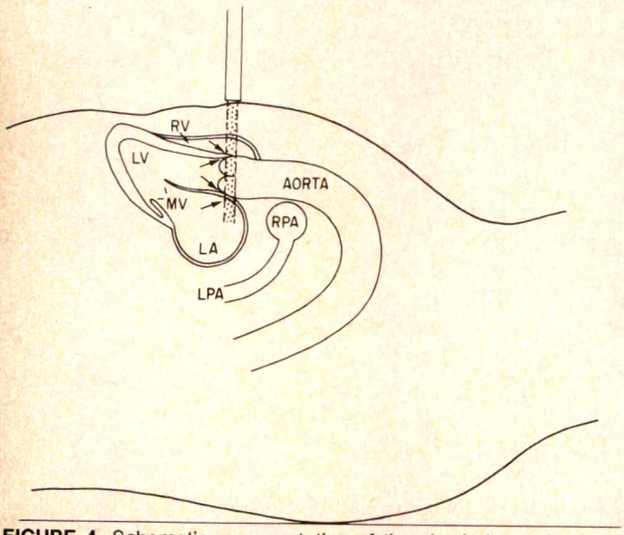

FIGURE 4. Schematic representation of theorized ultrasonic penetration through the aortic root producing the echocardiographic features of a false dissecting hematoma. The transducer position is more cephalad on the chest wall than usual. The beam passes through the fibrous aortic root-membraneous ventricular septum and fibrous aortic root-mitral (MV) junctures. Resulting echoes from the anterior and posterior sides of each of these junctures may explain the "false dissecting hematomas" described in this report. Variations in the beam angle would result in variable aortic root width as the sinuses of Valsalva and other structures were examined. LA = left atrium; LPA = left pulmonary artery; LV = left ventricle; RPA = right pulmonary artery; RV = right ventricle.

this anomaly. However, the echocardiographic pattern of aortic dissection was also noted in 5 of the 10 patients with no clinical indication of aortic root dissection. These five patients had (1) aortic root dilatation (42 mm or more at end-systole); (2) a thickened *posterior* aortic wall (10 mm or more at end-systole); and (3) maintenance of parallel motion of the separated margins of the aortic walls. The remaining five patients in our series met at least two of the three criteria for aortic root dissection. Four had a thickened posterior aortic wall and parallel motion of the separated margins of the widened walls, and one had aortic root dilatation and parallel motion of a posterior aortic wall that was a borderline indication of enlargement (8 mm at end-systole). In addition, 3 of the 10 patients studied had an abnormally thick anterior aortic wall (10 to 12 mm)[4] although in none was it as thick as in patients with aortic root dissection (16 to 21 mm)[1] (Fig. 2). As in aortic root dissection, the echocardiograms of all patients in this series revealed some variation in the width of the aortic root or aortic wall thickness, or both, with slight change in the direction of the transducer (Fig. 3).

One possible explanation for our findings lies in the angle of beam penetration through the fibrous aortic ring. As seen in Figure 4, it is easy to theorize a path of penetration in which an echo is obtained from each side of the aortic-mitral junction. An echocardiogram from this region could demonstrate a false double lumen if the movement plane of the region were almost perpendicular to the sound beam so as to allow reflected echoes from it to return to the transducer. This theory would offer some explanation for both the absence of these findings in the majority of patients and the change in aortic root width as the transducer angle is changed (Fig. 3). Angulation through various portions of the aortic ring and sinuses of Valsalva might mimic variations in aortic root thickness that occur in patients with aortic root dissection as a result of the nonuniform thickness of the dissecting hematoma.

Clinical implications: Perhaps the most useful findings previously reported in patients with aortic root dissection are a markedly thickened anterior wall (16 to 21 mm) and the presence of clinical indications of the disorder. No patient in this series without aortic root dissection had an anterior aortic wall thickness as great as that found in aortic root dissection, whereas 9 of the 10 patients without clinical indication of this disorder had a thickened posterior aortic wall. Echocardiographic patterns mimicking aortic root dissection were found in only 1 to 2 percent of the patients studied in this laboratory without clinical indication of the disorder. When there is a clinical indication of dissection, echocardiography is probably a very helpful means of detecting the aortic root dissection if (1) the *anterior* aortic wall is at least 16 mm thick, (2) parallel motion between the inner and outer borders of the thickened wall is maintained throughout the cardiac cycle, (3) the aortic root is dilated (42 mm or more), and (4) the clinical course of the patient is consistent with aortic root dissection.

When aortic root dissection is present, we believe that echocardiography is a useful tool in detecting it. However, the echocardiographic pattern of aortic root dissection is sometimes seen when there is no clinical indication of the disorder. Therefore, those performing ultrasonic studies should be wary of making the diagnosis on the basis of the echocardiographic pattern unless the clinical history is suggestive of dissection. This caution could prevent unnecessary invasive studies in some cases.

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Echocardiographic Differentiation of Infundibular from Valvular Pulmonary Stenosis

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Echocardiographic tracings of the pulmonary valve were examined in 24 normal subjects, 16 patients with valvular pulmonary stenosis and 3 patients with infundibular pulmonary stenosis. In normal subjects, atrial contraction produced a slight posterior or opening motion of the pulmonary valve leaflet (*a* wave). This presystolic opening motion (*a* wave) varied with respiration, and maximal *a* wave depth recorded during quiet inspiration (*A*max) averaged 3.7 ± 1.2 (standard error of the mean) mm (range 2 to 7 mm). In the 10 cases with moderate or severe valvular pulmonary stenosis, increased force of right atrial contraction and elevated right ventricular end-diastolic pressure resulted in an increased posterior or opening motion of the pulmonary valve leaflet, and *A*max averaged 9.6 ± 2.0 mm (range 8 to 13 mm, $P < 0.001$ versus normal). When both anterior and posterior leaflets were recorded, presystolic opening or doming of the valve was observed. In six cases of mild valvular pulmonary stenosis, *A*max averaged 4 ± 2.5 mm (not significant). In patients with infundibular pulmonary stenosis, marked chaotic systolic fluttering of the valve leaflet, which lies in the turbulent stream of blood distal to the obstruction, was recorded. This finding was never seen with valvular pulmonary stenosis. In two cases of mild infundibular pulmonary stenosis, the amplitude of presystolic opening motion was within the normal range of 3 and 7 mm. In one case of severe infundibular pulmonary stenosis, no presystolic opening motion was recorded, thus suggesting that the small pressure changes produced by atrial systole failed to reach the valve leaflets. Echocardiography, therefore, should be of use in differentiating valvular from infundibular pulmonary stenosis.

Obstruction to right ventricular outflow may occur at the valvular, infundibular or subinfundibular level.[1] Valvular pulmonary stenosis is characterized by conical or dome-like fusion of the pulmonary valve cusps with a central perforation at the apex. Infundibular pulmonary stenosis may result from either a discrete fibrous band at the entrance to the right ventricular outflow tract with post-stenotic dilatation of the infundibular chamber or more generalized hypertrophy of the infundibular musculature with resultant obstruction.[2] Subinfundibular stenosis is a relatively rare variety of right ventricular outflow obstruction caused by hypertrophic muscle bundles within the right ventricular cavity that tend to separate the inflow from the outflow portions of the ventricle.[3,4]

The diagnostic value of the echocardiographic motion of the pulmonary valve has been suggested in several recent reports.[5,6] We have been interested in examining the pulmonary valve for the diagnosis of valvular pulmonary stenosis.[7] While examining a large group of patients with clinically suspected pulmonary stenosis, we observed three in whom the pattern of pulmonary valve echocardiographic motion differed markedly from that which we had previously observed

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in valvular pulmonary stenosis. In each of these three cases the obstruction to right ventricular outflow was determined to be at the infundibular level. This report describes the pattern of pulmonary valve motion seen with infundibular pulmonary stenosis and compares it with the pattern observed in valvular pulmonary stenosis.

Materials and Methods

Echocardiographic tracings of the pulmonary valve were examined in three female patients with infundibular pulmonary stenosis. Their ages were 10, 18 and 19 years, respectively. The diagnosis of infundibular pulmonary stenosis was made on the basis of a pressure gradient across the right ventricular outflow tract with no gradient at the valvular level and the typical appearance of the lesion on cineangiograms. In Case 1, the peak systolic gradient was 48 mm Hg. In this case the infundibular obstruction was associated with a small muscular ventricular septal defect with a 1.2:1 left to right shunt that was not considered hemodynamically significant. In Case 2, a catheter could not be passed beyond the infundibular obstruction and the diagnosis was made on the basis of the angiographic demonstration of an area of narrowing of the right ventricular outflow tract proximal to the pulmonary valve with normal mobility of the valve itself, and a right ventricular systolic pressure of 43 mm Hg. In Case 3, the peak systolic gradient was 113 mm Hg. In no case was associated valvular pulmonary stenosis believed to be present. The pattern of pulmonary valve motion observed in these 3 patients was then compared with the valve motion observed in 24 normal patients and 16 patients with valvular pulmonary stenosis. Of the latter 16 patients, 6 had mild stenosis (gradient less than 50 mm Hg), 6 had moderate stenosis (gradient 50 to 100 mm Hg) and 4 had severe stenosis (gradient more than 100 mm Hg).

The echocardiographic examination was performed with an Ekoline 20A echograph combined with either a Honeywell model 1856 fiberoptic strip chart recorder or an Electronics for Medicine recorder. A 2.25 megahertz transducer with an outer diameter of 1.25 cm focused at 7.5 cm was used. Several techniques for examining the pulmonary valve have previously been described. The first approach, described by Gramiak et al.,[5] is to locate the aortic valve and then, either by angling the transducer cephalad or by moving the transducer one interspace higher, to locate the supravalvular portion of the aorta. From this high left parasternal position, the beam is angled in a lateral and cephalad direction. As the image of the aortic wall disappears, the pulmonary artery becomes visible as an echo-free space anterior to the aorta with its anterior border within 1 to 2 cm of the lower margin of the chest. The posterior margin of the pulmonary artery is characteristically visualized as a wide band of echoes that may lie 2 to 4 cm behind the anterior margin of the artery. The pulmonary valve cusps appear as thin lines that move within the margin of the pulmonary artery.

The second approach[7] is to locate the mitral valve, then tilt the transducer superiorly and slightly toward the throat, but not far enough to record the aorta. As the ultrasonic beam leaves the left ventricular cavity, a dense mass of echoes will be recorded from the region of the right ventricular outflow tract and the potential space between the pulmonary artery and the left atrium. Continuing cephalad, the echo-free pulmonary artery again will appear 1 to 2 cm below the anterior chest wall. The valve leaflets are then located by gentle scanning within the pulmonary artery. Finally, we have noted that, in patients in whom a pulmonary arterial impulse can be palpated along the left sternal border, placing the transducer directly over this impulse permits ready detection of the pulmonary valve.[8] In each of the three cases of infundibular stenosis a complete echocardiographic examination including a recording of the tricuspid valve was performed in addition to the pulmonary valve study. The posterior pulmonary and anterior tricuspid leaflets were clearly recorded in each case. Respiration was timed by an independent observer and the tracing marked for the duration of inspiration.[9]

Because only one pulmonary valve leaflet is usually recorded, the exact duration of right ventricular ejection cannot be determined from the pulmonary valve echo alone. Since tricuspid valve opening represents the onset of right ventricular diastole and follows the termination of right ventricular ejection and normal pulmonary valve closure, we attempted to relate the point of tricuspid valve opening to the pulmonary valve echo to determine the expected limit of right ventricular ejection. To do this, the duration from the onset of tricuspid valve opening to the Q wave of the following QRS complex of the electrocardiogram was measured. This measurement was then used to determine the point of tricuspid valve opening in pulmonary valve complexes of similar cycle length. This point slightly overestimates the point of pulmonary valve closure since it fails to allow for isometric relaxation. However, any motion of the leaflet continuing beyond this point will obviously extend into the diastolic period of the right ventricle.

Results

The Normal Pulmonary Valve

Figure 1A illustrates a normal posterior pulmonary valve leaflet recorded throughout several cardiac cycles. Because of the position of the pulmonary valve in the chest and its plane of motion relative to the ultrasonic beam, the echocardiogram usually records only one posterior pulmonary valve leaflet. The lettering in this figure is similar to that previously described.[7] The *a* wave that follows the P wave of the electrocardiogram reflects the effect of atrial contraction on the pulmonary valve leaflet. That this wave is due to atrial contraction has been confirmed by its constant relation to the P wave in complete heart block and its disappearance with atrial fibrillation. In normal patients the *a* wave depth increases during inspiration. In 24 normal subjects, the maximal depth of the *a* wave recorded during quiet respiration (*A*max) was 3.7 ± 1.2 (standard error of the mean) mm (range 2 to 7 mm).

After atrial contraction, the leaflet normally returns to an initial or closed position (point b) prior to the onset of ventricular ejection. In patients with deep inspiratory *a* waves, particularly when the P-R interval is short, ventricular ejection may occur with the leaflet still partially open. From point b, (the position of the valve at the onset of ventricular ejection), the leaflet moves rapidly to a fully open position (point c).

During systole there is a gradual anterior movement of the leaflet (c-d) followed by rapid diastolic closure of the valve (d-e). During diastole, the leaflet moves gradually posteriorly to point f, which precedes the onset of atrial systole. The anterior systolic

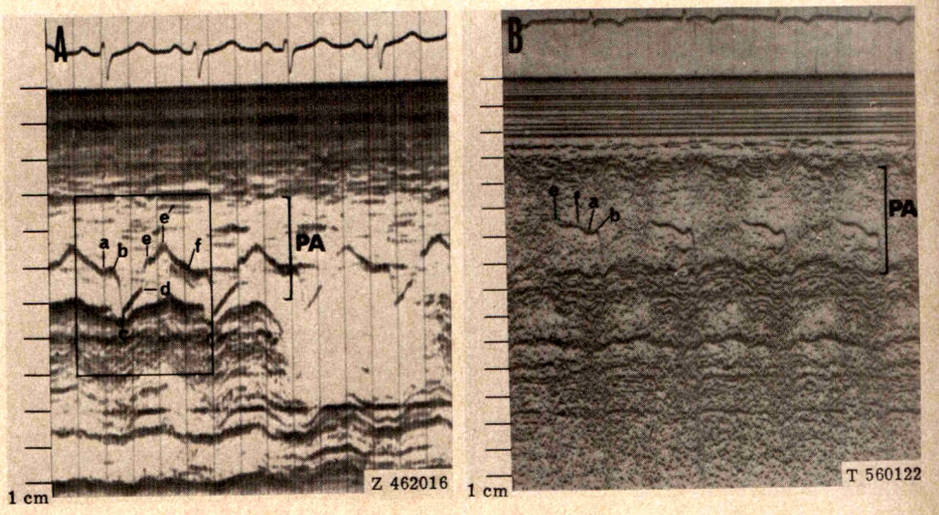

FIGURE 1. Normal. **A,** a normal posterior pulmonary valve leaflet recorded throughout several cardiac cycles. The *a* wave that follows the P wave of the electrocardiogram reflects the effect of atrial contraction of the pulmonary valve leaflet. Point b = the position of the leaflet at the onset of ventricular ejection; b-c = rapid systolic opening of the leaflet; c-d = the leaflet in the open position during systole; d-e = diastolic closure; e-f = leaflets in the closed position during diastole; e-e′ is a variable finding and probably represents transmitted pulsations from the aorta. **B,** a more characteristic normal recording. See text. PA = pulmonary artery.

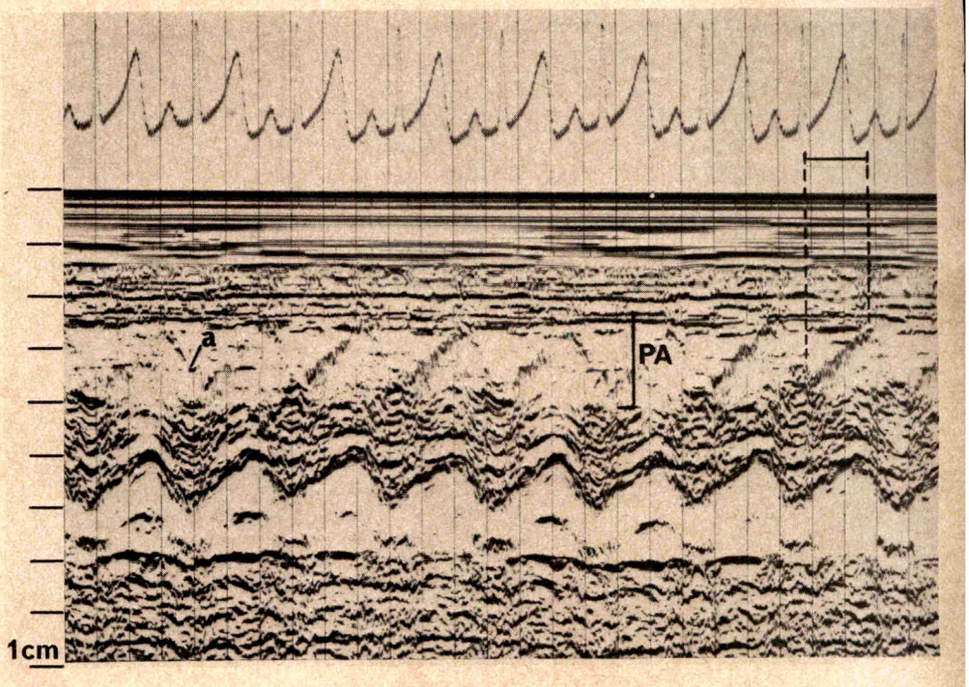

FIGURE 2. Case 1. Mild pulmonary infundibular stenosis. See text.

(c-d) and posterior diastolic (e-f) slopes of the leaflet probably represent pulsatile movement of the pulmonary artery and valve apparatus. In Figure 1A there is further anterior motion from point e-e′. This is a variable finding and may represent transmitted pulsations from the aorta.

Whereas in Figure 1A the leaflet is recorded throughout the cardiac cycle, Figure 1B represents the more characteristic normal recording. In this tracing, the e-f slope, *a* wave and b point are clearly seen. However, as the leaflet approaches the fully open position (point c) it is lost in the dense mass of echoes recorded from behind the pulmonary artery. In these cases, point c, together with the c-d slope and diastolic closure (d-e), is not appreciated. When the leaflet is recorded during systole in normal subjects, the c-d segment is straight. In two of these normal subjects, very fine fluttering of this segment was observed.

Infundibular Pulmonary Stenosis

In the three cases of infundibular pulmonary stenosis, a characteristic pattern of pulmonary valve motion was observed during systole. In each case, the posterior pulmonary valve leaflet opened normally with the onset of ventricular ejection. However, immediately upon reaching the fully open position, the leaflet began a gross high-frequency fluttering that continued throughout systole and into diastole. In each case, cycles occurred where this fluttering was interrupted only by the next atrial contraction.

The magnitude of the *a* wave reflecting the effect of atrial systole on the pulmonary valve was also examined in these cases. In Cases 1 and 2 (mild steno-

sis), *A*max, or the maximal depth of the *a* wave recorded during normal inspiration, was within the normal range of 2 to 7 mm (7 and 3 mm, respectively). In Case 3 (severe stenosis), no *a* wave was recorded.

Figure 2 illustrates a posterior pulmonary valve leaflet recorded from Case 1 (mild infundibular pulmonary stenosis). On the left of the tracing a normal *a* wave (7 mm) is recorded. After the *a* wave, the valve opens rapidly with systolic ejection. Immediately upon reaching a fully open position, the leaflet begins a high-frequency fluttering that continues throughout systole and into diastole, being terminated only by the next *a* wave (atrial contraction). The duration of fluttering in relation to the electrocardiogram is shown between the interrupted lines in the last complex. In this case, we were unable to record the leaflet throughout the cardiac cycle from one transducer position. In this figure, the duration and amplitude of the systolic fluttering are clearly seen; however, the *a* wave and systolic opening of the valve are poorly recorded. In Figure 3, from the same patient, the *a* wave and systolic opening of the leaflet can be clearly seen. In addition, the normal respiratory variation in *a* wave depth is apparent. However, in this recording, the leaflet is lost in the latter part of systole and the extension of the fluttering into diastole is not appreciated.

Figure 4 is a recording from Case 2 (mild infundibular stenosis). A normal *a* wave (3 mm) and high-frequency, very coarse fluttering of the posterior pulmonary valve leaflet are again seen.

Figure 5 is a recording from Case 3 (severe infundibular stenosis). No *a* wave is present and, again, coarse systolic fluttering extending well into diastole is observed. The fluttering in this case is of a similar amplitude, but lower frequency than that seen with mild stenosis. As in the other two cases, this fluttering was frequently observed to continue into diastole.

Valvular Pulmonary Stenosis

In the six cases with mild valvular pulmonary stenosis (gradient less than 50 mm Hg), *A*max averaged 4 mm (range 1 to 8 mm) (difference not significant from normal). In patients with moderate and severe pulmonary stenosis, a marked increase in *a* wave depth was observed. In these 10 cases *A*max averaged 9.6 ± 2 mm (range 8 to 13 mm) ($P < 0.001$). In none of these cases was the systolic c-d segment or diastolic closure (d-e) of the posterior leaflet recorded.

Discussion

Systolic fluttering of the pulmonary leaflet in infundibular stenosis: The characteristic finding in the three patients with infundibular pulmonary stenosis was a high-frequency, coarse systolic fluttering of the pulmonary valve leaflet. This fluttering very likely results from the turbulent stream of blood distal to the infundibular obstruction striking the pulmonary valve. Whereas turbulence distal to a point of obstruction will induce vibration in any mobile structure exposed to it, this vibration is especially prominent in poorly supported structures such as valve leaflets. In patients with discrete membranous subaortic stenosis a similar situation occurs. In these

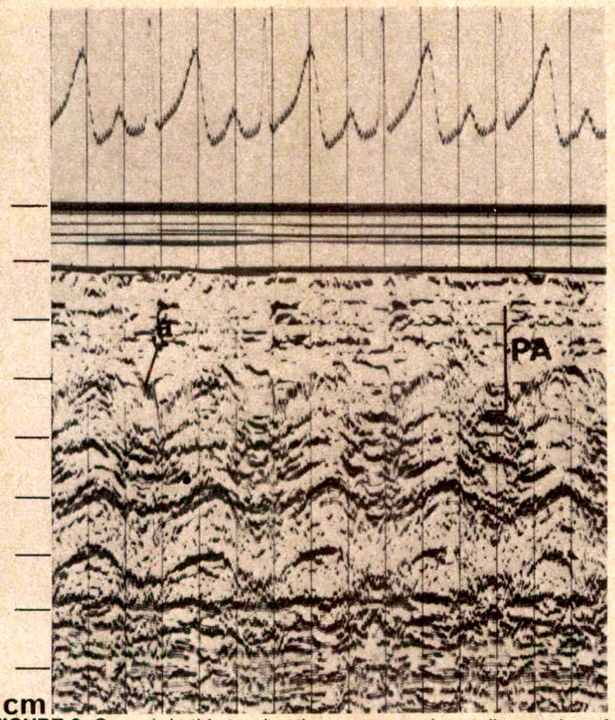

FIGURE 3. Case 1. In this tracing the *a* wave and systolic opening of the leaflet are more clearly seen and the normal respiratory variation in *a* wave depth is apparent. In the first complex on the left, obtained during inspiration, a 5 mm *a* wave is recorded. Fluttering of the leaflet during atrial contraction is also apparent, implying turbulent flow of blood distal to the infundibular obstruction during atrial systole.

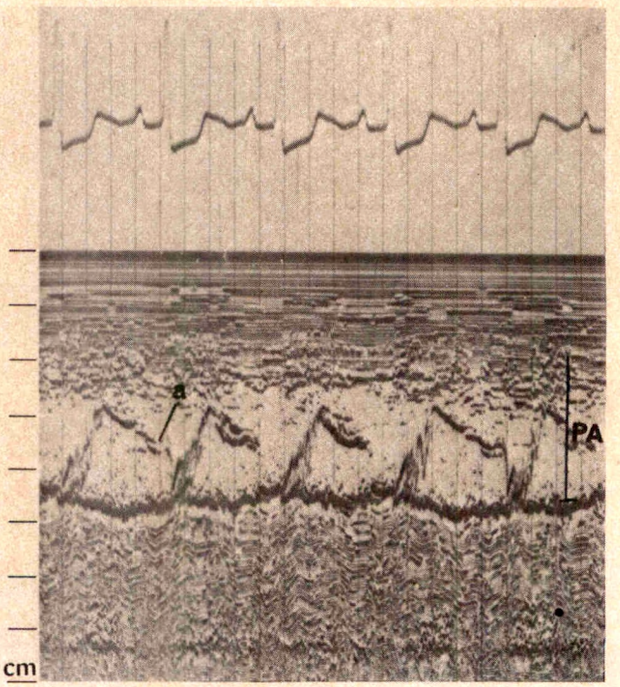

FIGURE 4. Case 2. Mild infundibular stenosis. See text.

cases the aortic leaflets lie within the turbulent stream of blood distal to the area of obstruction, and systolic vibrations or fluttering of these leaflets has been described.[10] In left-sided lesions this vibration or fluttering is limited to the period of systolic ejection and terminates with valve closure.[10] In each of the three cases of infundibular pulmonary stenosis, the fluttering appeared to extend well beyond the expected end of ventricular ejection. Since both pulmonary valve leaflets are ordinarily not recorded, we were unable to determine the end of ventricular ejection directly from the point of pulmonary valve closure. However, by determining the point of tricuspid valve opening at similar cycle lengths, we were able to establish end-systole or beginning diastole in the right ventricular chamber. When this point was related to the duration of fluttering, it was evident that fluttering continued well into diastole in each case, frequently being interrupted by the atrial contraction of the next cycle. The exact duration of fluttering beyond the termination of right ventricular systole could not be determined because of the lack of a precise point at which fluttering terminates and the failure of our method to allow for isometric contraction and relaxation.

Hemodynamic basis for pulmonary leaflet fluttering: If fluttering is due to turbulent blood flow and this fluttering continues into diastole, then con-

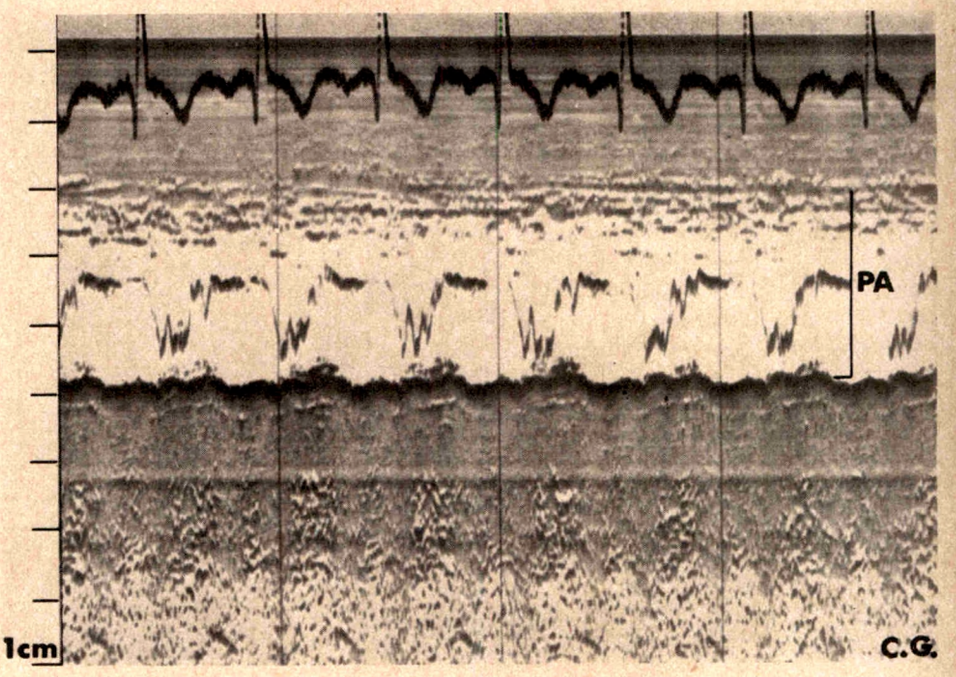

FIGURE 5. Case 3. Severe infundibular stenosis. See text.

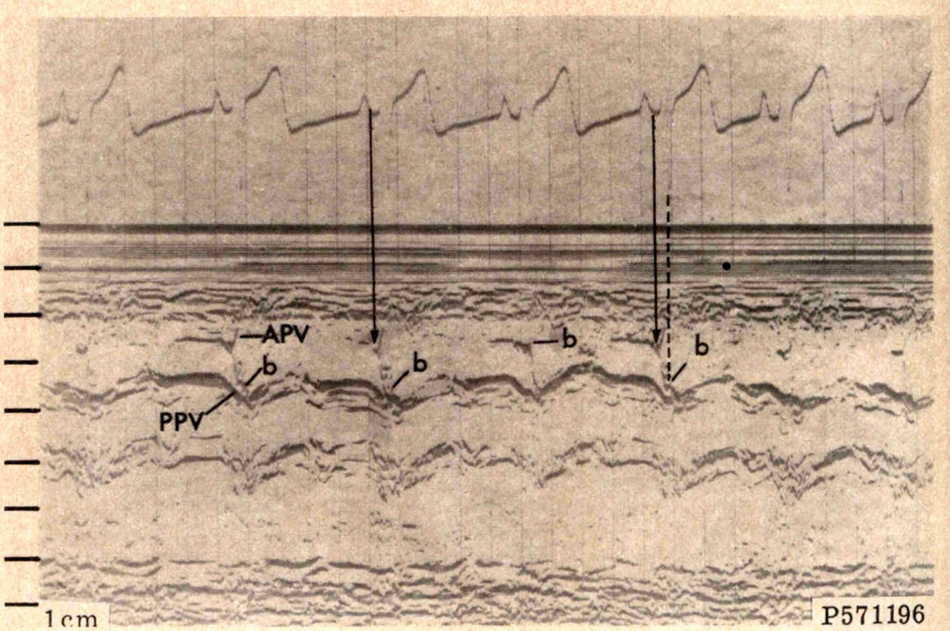

FIGURE 6. Case with valvular pulmonary stenosis. Large inspiratory *a* waves can be appreciated after atrial systole (**solid vertical arrows**) in the first, second and fourth complexes from the left. In these three complexes ventricular systole (interrupted line, fourth complex) occurs with the leaflets in an almost fully open position (point b). In addition, the anterior pulmonary valve leaflet (APV) can be seen to separate from the posterior leaflet and move anteriorly after atrial systole, indicating that the large *a* waves do reflect opening or doming of the valve. In the third complex recorded during expiration, a normal *a* wave is present, and ventricular systole occurs with the valve in a closed position (point b). APV = anterior pulmonary valve; PPV = posterior pulmonary valve; point b = position of the valve at the onset of ventricular systole.

tinued diastolic flow from the infundibular chamber into the pulmonary artery might be implied. In these cases, the leaflets did return to an initial and presumably closed or nearly closed position during diastole, thus suggesting that if there was continued flow across the valve it was of small volume. In addition, the amplitude of fluttering decreased during this period. Vogelpoel and Schrire[11] demonstrated that pulmonary valve closure occurred later in patients with infundibular pulmonary stenosis than in patients with valvular pulmonary stenosis with similar gradients. They recorded a duration from aortic to pulmonary valve closure of up to 0.14 second in patients with severe infundibular stenosis. By comparing pressure curves from the right ventricular and infundibular cavities in patients with tetralogy of Fallot, these authors[12] also demonstrated that systole continued for a longer period in the infundibular chamber than in the body of the right ventricle. They postulated that the prolongation of right ventricular systole as measured by the delayed closure of the pulmonary valve was in fact due to late contraction of the infundibular chamber. Since the infundibular chamber empties into the low pressure pulmonary arterial system, the occurrence of some diastolic flow with resultant fluttering or vibration of the leaflet would not be surprising. Alternatively it is possible that the high-frequency vibrations in the valve leaflets during systole are poorly damped by the low pulmonary arterial pressures distal to the valve and continue well into diastole.

Differentiation from valvular pulmonary stenosis: The pattern of pulmonary valve motion observed in infundibular pulmonary stenosis is sufficiently different from that observed in valvular pulmonary stenosis to permit ready differentiation of the two lesions. In valvular pulmonary stenosis, the characteristic changes are related to the magnitude or depth of the *a* wave of the posterior pulmonary valve leaflet. The *a* wave has been shown to be caused by right atrial contraction, and its depth is thought to be related to the simultaneous pressures existent across the pulmonary valve at peak right ventricular end-diastolic pressure after atrial contraction. In mild valvular pulmonary stenosis, a normal *a* wave has been observed (average 4 mm). In moderate and severe valvular pulmonary stenosis, the increased force of right atrial contraction and increase in right ventricular end-diastolic pressure occurring with a normal or low pulmonary arterial pressure frequently produce a positive end-diastolic gradient across the valve that results in marked augmentation in *a* wave depth (average 9.6 mm). When both anterior and posterior leaflets are recorded simultaneously after atrial systole, the anterior leaflet separates from the posterior leaflet and moves anteriorly. This indicates that these large *a* waves represent presystolic opening or "doming" of the valve (Fig. 6). In addition, we have observed no fluttering of the leaflet during systole in patients with valvular pulmonary stenosis. This absence of fluttering is to be expected since in valvular pulmonary stenosis the turbulent stream occurs distal to the obstruction and should not affect the valve itself.

***A* wave in infundibular versus valvular stenosis:** In the two cases of mild infundibular stenosis, a normal *a* wave was recorded. This is similar to our findings in mild valvular stenosis and we believe that it represents the lack of significant hemodynamic changes produced by mild lesions. However, in the case with severe infundibular stenosis, no *a* wave was recorded. This is the exact opposite of the situation with severe valvular stenosis and may imply that the severe obstruction below the valve prevents the relatively small pressure change caused by atrial contraction from reaching the valve with enough force to produce movement of the leaflets. This suggests then that, whereas the *a* wave in valvular pulmonary stenosis grows increasingly larger as the lesion becomes more severe, the opposite may occur in infundibular stenosis, with the *a* wave becoming smaller and finally disappearing as the degree of obstruction increases. In addition, although normal *a* waves are seen in both mild valvular and mild infundibular stenosis, chaotic systolic fluttering of the valve leaflet extending into diastole is seen only with infundibular stenosis. Therefore, when pulmonary stenosis is suspected clinically, these echocardiographic findings should serve to distinguish the two lesions.

Acknowledgment

We thank Dr. Charles Wunsch and Community Hospital, Indianapolis, Ind. for the data on the patient with severe infundibular pulmonary stenosis.

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Radiographic Appearance of the Thorax in Systolic Click-Late Systolic Murmur Syndrome

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The posteroanterior and lateral chest X-ray films of 64 consecutive patients with an isolated systolic click (55 patients) or a systolic click with a late systolic murmur (9 patients) showed a striking frequency of thoracic skeletal abnormalities. There were 50 female and 14 male subjects. The average age of the female subjects was 36.7 years (range 13 to 67), that of the male subjects 39.7 years (range 17 to 56). Seventy-two percent of the female and 78 percent of the male subjects had an anteroposterior/transverse thoracic ratio less than the mean ratio in a normal population. Bony abnormalities such as pectus excavatum, straight thoracic spine and scoliosis occurred alone or in combination in 31 of the 50 female patients (62 percent) and in 8 of the 14 male patients (57 percent). Overall, 39 of the 64 patients (61 percent) had at least one of the skeletal abnormalities. Scoliosis occurred in 25 subjects (39 percent) and was mild in 19. A "straight back" was found in 15 (23 percent) and pectus excavatum in 7 patients (11 percent). The explanation for these findings is not apparent. Thoracic cage abnormalities should be included as one of the nonauscultatory features of the systolic click-late systolic murmur syndrome.

Patients with an apical isolated systolic click or a systolic click together with a late systolic murmur have many clinical features in common. In addition to the auscultatory characteristics (clicks and murmurs), certain nonauscultatory features occur with such frequency that they collectively constitute a distinct syndrome. These features are unusual forms of chest pain; palpitations; anxiety; lightheadedness; dyspnea; atrial or ventricular arrhythmias, or both; electrocardiographic T wave changes and, occasionally, Q waves in the inferior leads; occasional familial incidence; and a tendency to occur more commonly in young women.[1–10] We have observed[11] still other common characteristics in this group: a tendency to narrow anteroposterior dimensions of the chest and a high frequency of mild thoracic scoliosis, pectus excavatum or a loss of normal dorsal kyphosis of the thoracic spine. This study reports these patterns of chest configuration as seen in X-ray films of the chest.

Material

Sixty-four consecutive outpatients, referred for evaluation of a systolic click or a click with a late systolic murmur, had a complete history, physical examination, 12 lead electrocardiogram, phonocardiogram and X-ray examination of the chest in posteroanterior and lateral projections.

The films were reviewed for the presence of thoracic scoliosis and pectus excavatum and for the decrease or absence of normal thoracic kyphosis ("straight back"). Internal dimensions of the chest were recorded in the lateral view, from the anterior surface of the body of the eighth thoracic vertebra along a perpendicular line to the posterior cortex of the sternum; in the posteroanterior view, the transthoracic diameter was measured at the level of the diaphragm. The ratio of the anteroposterior to the transthoracic dimen-

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sion was obtained. Thoracic cage dimensions in 100 normal subjects, 50 men and 50 women of similar age, have previously been reported and were used for comparison.[12]

Results

Of the 64 subjects studied, 55 had an isolated systolic click, and 9 had a click with a late systolic murmur. In 24 (44 percent) of the 55 patients with an isolated click, a late systolic apical murmur did develop with provocative maneuvers, such as standing erect, exercise, the Valsalva maneuver or the infusion of a vasopressor. There were 50 female and 14 male subjects.

The 50 female subjects ranged in age from 13 to 67

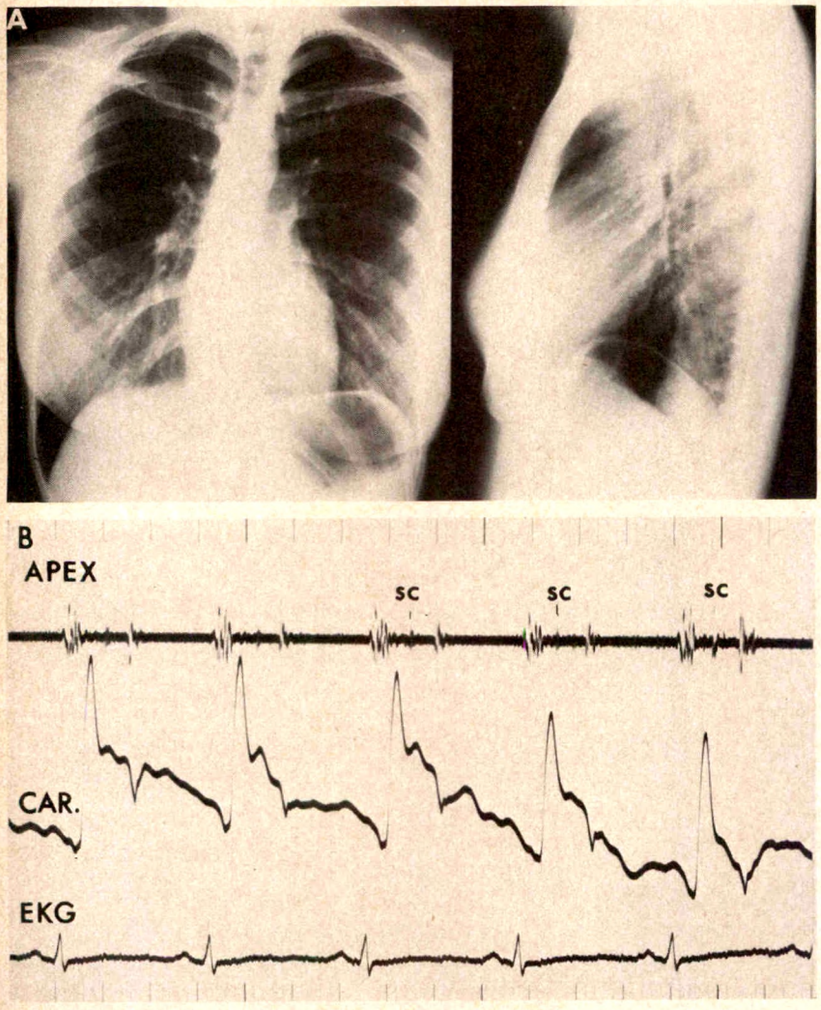

FIGURE 1. Patient with severe scoliosis of spine and mid-systolic click. **A,** chest X-ray film in posteroanterior and lateral projections. **B,** phonocardiogram. APEX = apex phonocardiogram; CAR. = carotid pulse tracing; EKG = electrocardiogram; sc = systolic click.

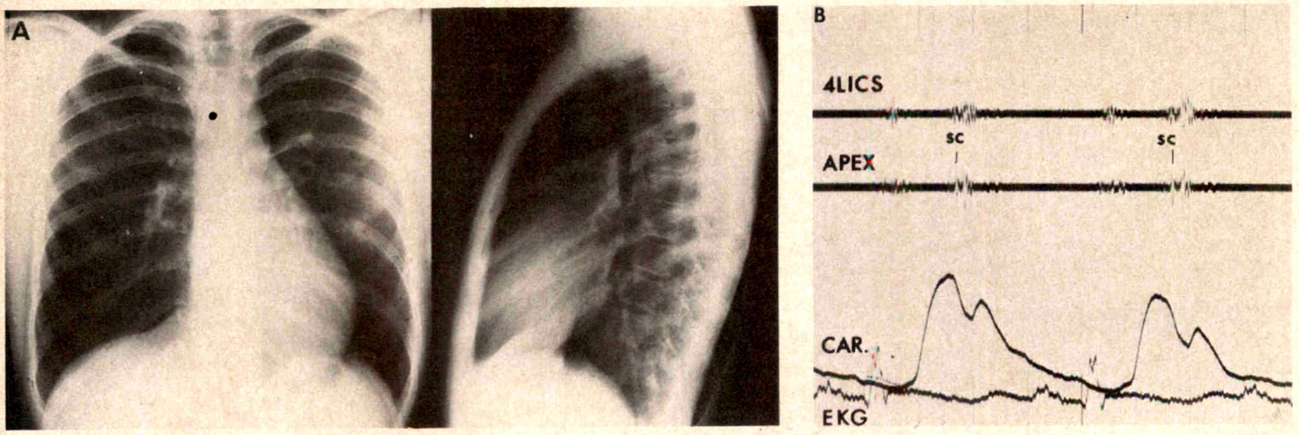

FIGURE 2. Patient with mild thoracic scoliosis and late systolic click and murmur. **A,** chest X-ray film in posteroanterior and lateral projections. **B,** phonocardiogram. In most patients with scoliosis, the condition was mild. 4 LICS = fourth left intercostal space.

TABLE I

Thoracic Skeletal Abnormalities in Patients with a Systolic Click or a Systolic Click with a Late Systolic Murmur

	Patients					
	Female		Male		Total	
	no.	%	no.	%	no.	%
Number	50		14		64	
Age (yr)						
Range	13–67		17–56		13–67	
Average	36.7		39.7		37.4	
Scoliosis	20	40	5	36	25	39
"Straight back"	11	22	4	29	15	23
Pectus excavatum	7	14	0	0	7	11
Any of above	31	62	8	57	39	61

years (average 36.7) (Table I). In these subjects, the chest X-ray films revealed the following prevalence of the three specific chest configurations: scoliosis in 20 subjects (40 percent), "straight back" in 11 (22 percent) and pectus excavatum in 7 (14 percent). At least one of the three findings occurred in 31 of these subjects (62 percent). The average ratio of the anteroposterior dimension to the transverse dimension of the chest was 43 percent. Thirty-six female subjects (72 percent) had a ratio less than the mean ratio for normal women (45.7 percent) (Table II).

The 14 male patients ranged in age from 17 to 56 years (average 39.7) (Table I). Scoliosis was present in 5 (36 percent), "straight back" in 4 (29 percent) and pectus excavatum in none. The average anteroposterior/transverse ratio was 43 percent, and in 11 men (78 percent) this ratio was less than the mean ratio for normal men (47 percent) (Table II).

In the entire group of 64 subjects, 39 (61 percent) had at least one of the thoracic skeletal abnormalities; scoliosis was the most common defect, occurring in 25 subjects (39 percent) (Table I). It was moderate to severe (Fig. 1) in 6, and mild (Fig. 2) in 19. "Straight back" was observed in 15 patients (23 percent) (Fig. 3) and pectus excavatum in 7 (11 percent) (Fig. 4). Forty-seven subjects (73 percent) had an anteroposterior/transverse ratio less than the normal mean ratio for persons of their sex (Table II). Eight of the 64 patients (12.5 percent) had two of the bony thoracic abnormalities. None had the musculoskeletal or ocular manifestations typical of the Marfan syndrome.

TABLE II

Chest Configuration in 64 Patients with a Systolic Click or a Systolic Click with a Late Systolic Murmur

	Patients		
	Female	Male	Total
Mean anteroposterior/transverse thoracic ratio (%)			
Patients	43	43	...
Normal population	45.7	47	...
Patients with ratio less than the mean ratio in normal population			
Number	36	11	47
Percent	72	78	73

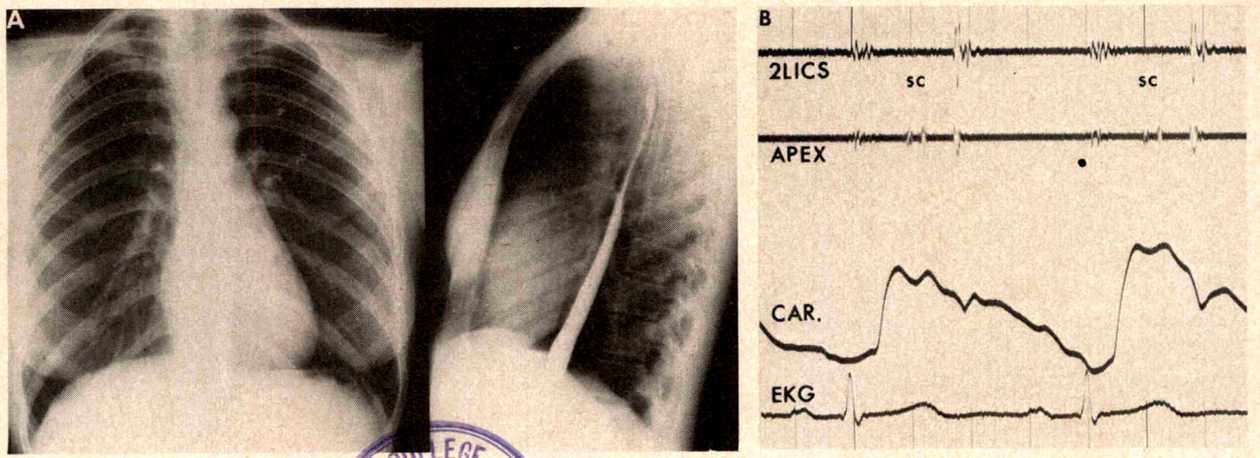

FIGURE 3. Patient with a straight thoracic spine, a mild pectus excavatum and multiple systolic clicks. **A,** chest X-ray film showing reduced anteroposterior dimension of the chest, although the generous space behind the heart excludes cardiac compression. **B,** phonocardiogram. 2 LICS = second left intercostal space.

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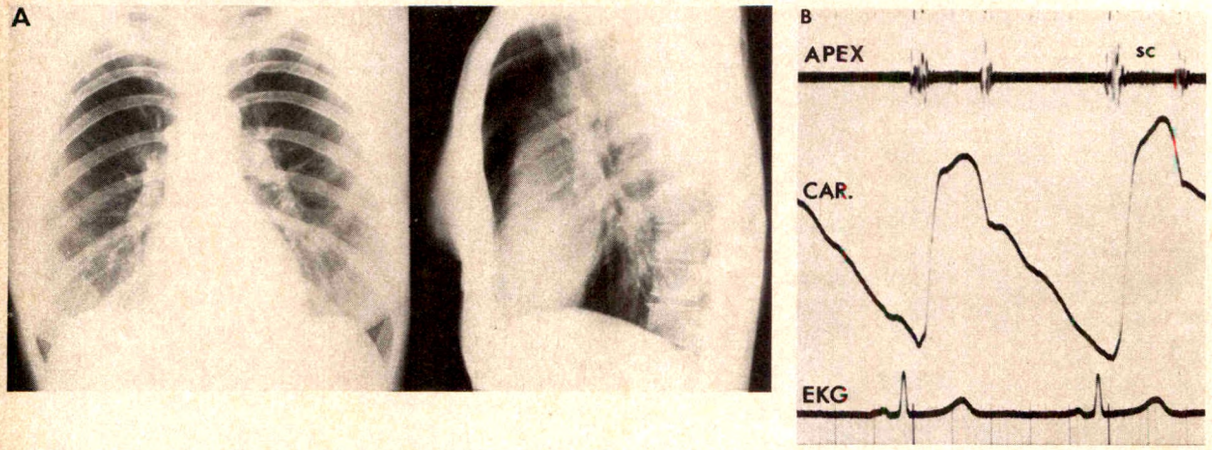

FIGURE 4. Patient with pectus excavatum and multiple systolic clicks. **A,** chest X-ray film in posteroanterior and lateral views. **B,** phonocardiogram.

Discussion

Prevalence of thoracic cage abnormalities: Abnormalities of the bony thorax are relatively common in the adult population. Although their presence does not imply associated cardiac disease,[13,14] some thoracic abnormalities, notably scoliosis and kyphosis, have been associated with other congenital anomalies, such as hiatus hernia.[15,16]

Narrow anteroposterior dimensions of the chest in mitral regurgitation have been previously noted, women with mild mitral regurgitation having been said to be "short, thin, and flat-chested."[16] The 73 percent rate of reduced anteroposterior/transverse thoracic ratios in our cases substantiates the typical "flatness" of the thorax in this population. Although measurements of body height and weight were not made, it has been our distinct impression that young patients with a systolic click and late systolic murmur are usually of slender build.

Thoracic abnormalities have been a point of interest in patients with a systolic click because these clicks were originally thought to be extracardiac in origin.[18–20] It was proposed that thoracic deformities might cause external compression of the heart, creating a clicking sound as the heart contracted and rotated during systole. However, the mitral valve origin of the clicks has been convincingly demonstrated by angiography,[21,22] echocardiography[23,24] and intracardiac phonocardiography,[25,26] and there is little evidence to substantiate their extracardiac origin.

Our data indicate that certain patterns of thoracic configuration are commonly seen in the systolic click-late systolic murmur syndrome. Twenty-five patients (39 percent) had scoliosis, and it was mild in 19. Fifteen subjects (23 percent) had lost the normal dorsal kyphosis of the thoracic spine and were said to have a "straight back." Seven patients (11 percent) had a pectus excavatum. Thirty-nine (61 percent) had at least one of these defects, and eight (12.5 percent) had two of the defects. None had a severe thoracic lesion. Despite the narrow internal anteroposterior dimension of the thorax, the heart was not "trapped" between the sternum and the spine in any case because there was adequate space either anterior or posterior to the heart. In no case did the thoracic configuration appear to be causing an extracardiac click.

The patients in this study were taken consecutively as they were referred for evaluation and thus represent a random sample of patients with the systolic click-late systolic murmur syndrome. They were predominantly young and female, as has been reported by others.[5,6] However, the male patients manifested all the thoracic abnormalities of the female patients, with the exception of pectus excavatum.

Embryologic basis for association of systolic click and thoracic abnormalities: The explanation for the correlation between the auscultatory findings in the syndrome and these types of thoracic configuration is not known. It has been suggested that patients with myxomatous changes in the mitral valve, some of whom had pectus excavatum or scoliosis, actually are manifesting a forme fruste of the Marfan syndrome, having a basic connective tissue disorder that leads to myxomatous changes in the mitral valve and skeletal abnormalities.[27,28] On the other hand, there may be an embryologic explanation for this coincidence of findings because the primordia of the mitral valve undergoes differentiation to its final form between the 35th and 42nd day of fetal development, at the time that the vertebral column and thoracic cage are beginning their chondrification and ossification.[28,29] Any influence on growth patterns at that stage of development might affect both the mitral valve and the bony thorax.

The nonauscultatory features that should be added to the findings commonly seen in the systolic click-late systolic murmur syndrome are a chest configuration with a narrowed anteroposterior dimension and the frequent occurrence of scoliosis, "straight back" and pectus excavatum.

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Thoracic Skeletal Abnormalities in Idiopathic Mitral Valve Prolapse

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Idiopathic prolapse of the mitral valve is a common disorder, but many cases are clinically subtle. Thoracic skeletal abnormalities, reported recently to accompany the syndrome, may serve as an easily identifiable clinical indicator. The prevalence of these abnormalities was defined in 24 patients with proved prolapse of the mitral valve. The valvular syndrome was defined clinically, by echocardiography and, in seven cases, by left ventricular angiography. The skeletal deformities were defined clinically and radiographically. Pectus excavatum was present in 62 percent of the patients, "straight back" in 17 percent and severe scoliosis in 8 percent. Eighteen of the 24 patients (75 percent) had a definite thoracic skeletal deformity. The association of idiopathic prolapse of the mitral valve with these skeletal deformities may represent a forme fruste of Marfan's syndrome. Patients with "straight back" and pectus excavatum should be examined clinically and perhaps by echocardiography to exclude idiopathic prolapse of the mitral valve; when murmurs are present, a diagnosis of "pseudoheart disease" should not be made before mitral valve prolapse has been excluded.

Since the earlier reports of Barlow et al.[1,2] describing a new syndrome of prolapse of the mitral valve, numerous communications have described its clinical,[3–5] pathologic,[6,7] echocardiographic[8,9] and angiographic[10–12] characteristics. The syndrome is now recognized with increasing frequency and is probably a very common disorder. The classic case presenting with nonejection click and late systolic murmur is readily identified. However, many cases are more subtle, and a high level of suspicion and various clinical maneuvers[4] are required to detect the click and the murmur, which may be variable[13] and evanescent. An easily identifiable clinical indicator is needed to suggest which patients may have mitral valve prolapse so that a more careful and complete examination is conducted. Thoracic skeletal abnormalities, which were reported recently to accompany mitral valve prolapse,[14,15] can serve as such an indicator. This report defines the prevalence of these skeletal abnormalities in our patients with prolapse of the mitral valve.

Material and Methods

The records were reviewed of all patients in the cardiology units of Strong Memorial Hospital and Rochester General Hospital from 1970 through 1972 who were found to have prolapse of the mitral valve. Patients with prolapse of known origin (Marfan's syndrome, rheumatic heart disease, coronary artery disease and chest trauma) were excluded. Twenty-four patients were found to have idiopathic prolapse of the mitral valve. Fourteen patients were female and 10 were male. The average age was 34 years (range 6 to 72). Clinical evaluation included assessment of the thoracic habitus (pectus excavatum, kyphoscoliosis, loss of the physiologic thoracic kyphosis, shallow chest) and auscultation in the supine and upright positions and during the Valsalva

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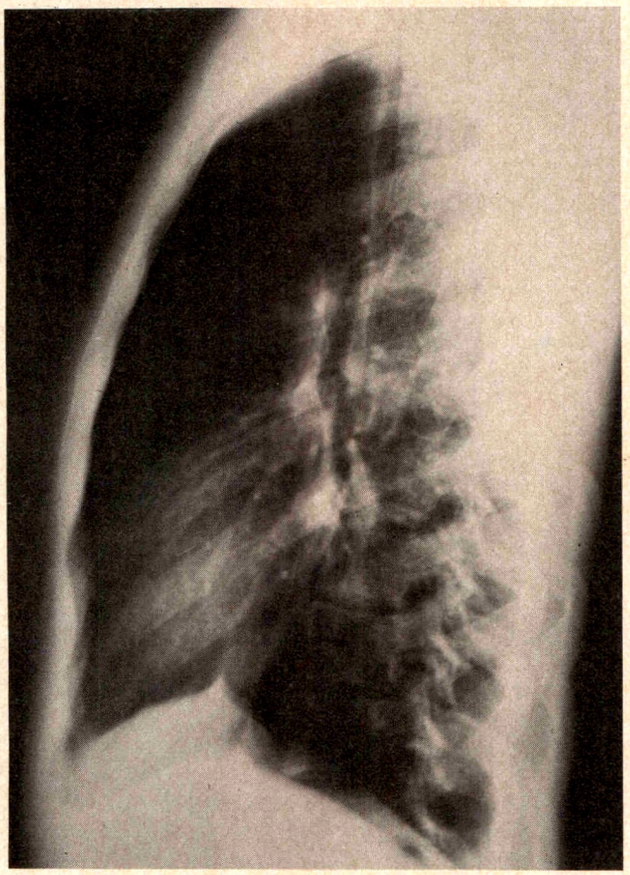
maneuver. Phonocardiograms were recorded in 21 patients. Standard posteroanterior and lateral chest X-ray films were obtained in each case. Anteroposterior diameter of the chest at the level of the eighth thoracic vertebra and transverse diameter at the level of the dome of the diaphragm were measured, and the ratio of the anteroposterior and transverse diameters was calculated. The presence of pectus excavatum was determined from the chest X-ray films and the condition was quantitated as either mild or severe. "Straight back" was defined by the following criteria: (1) loss of the physiologic thoracic kyphosis, and (2) anteroposterior diameter of the chest and anteroposterior



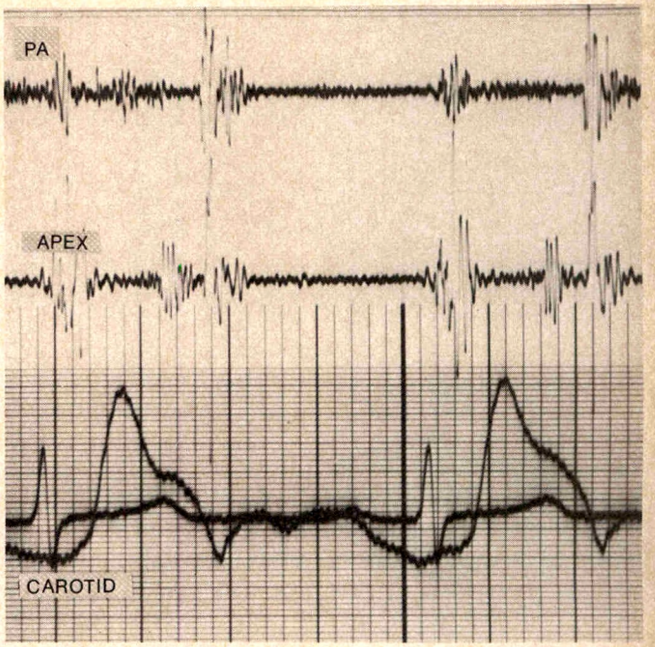
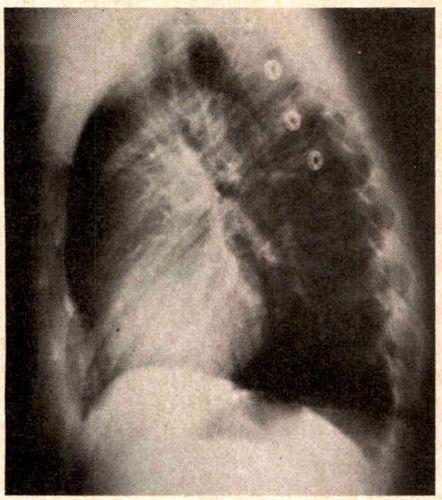


FIGURE 1. Case 16. **Left,** lateral chest X-ray film demonstrates a short anteroposterior diameter and loss of the physiologic thoracic kyphosis, the characteristic stigmata of "straight back". **Above,** phonocardiogram shows a nonejection click followed by a short late systolic murmur.



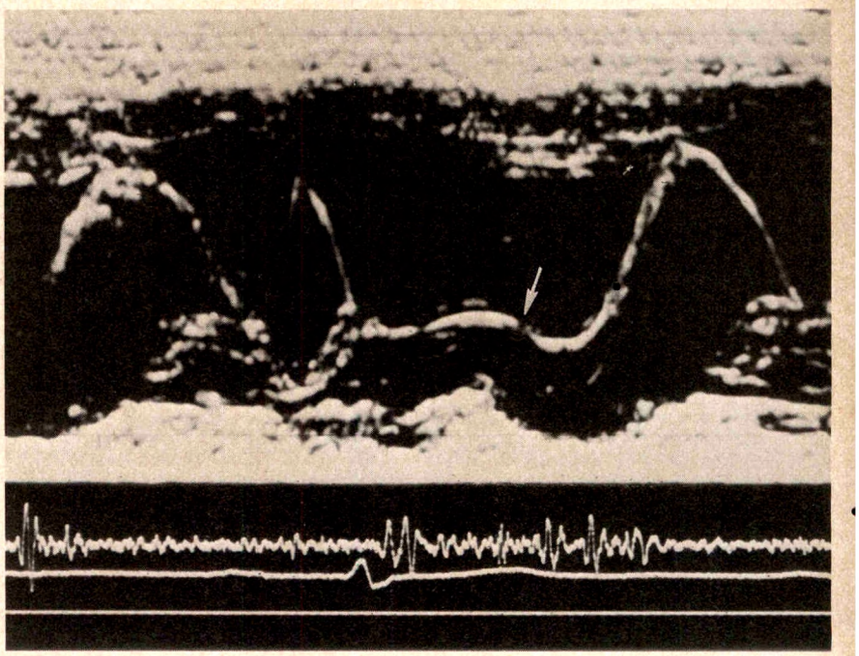


FIGURE 2. Case 2. **Above,** lateral chest X-ray film shows prominent pectus excavatum. **Right,** echocardiogram of mitral valve shows a posterior "step" in late systole, characteristic of mitral valve prolapse. The **arrow** marks the onset of the posterior displacement.

TABLE I

Clinical, Radiographic and Laboratory Data

Case no.	Age (yr) & Sex	Click	Murmur	Echo	Angio	Pectus	St. Back	AP/Trans.* cm	AP/Trans.* %	Comments
1	44F	+	+	MVP	...	+S	−	11.5/27	42	
2	35F	+	+	MVP	...	+M	−	13.5/29	46	
3	40F	+	+	MVP	...	+M	+	8.5/32	26	
4	46F	+	+	MVP	MVP	+M	−	10/25.5	39	
5	45F	+	+	MVP	MVP	+M	−	12.3/26.8	46	
6	35F	−	+	MVP	MVP	−	+	6.8/22.8	30	
7	18F	+	+	MVP	...	−	−†	10.5/25.5	41	
8	18F	+	+	MVP	...	−	−	12.5/27.7	45	
9	40F	+	−	MVP	...	+M	−	15.1/26	58	
10	26F	+	+	MVP	...	+M	−†	11/27.5	40	Loss of thoracic kyphosis
11	35F	−	+	...	MVP	+M	−	8/24.6	32	
12	27F	+	+	MVP	...	+S	−	11.6/25.6	45	
13	6F	−	+	MVP	...	−	−	...	...	Severe scoliosis
14	27F	+	+	MVP	...	+S	−	11/29.2	38	
15	24M	+	+	MVP	MVP	−	−†	13.6/32.6	42	Anterior flaring of lower thoracic cage
16	19M	+	+	MVP	MVP	+S	+	9/32	28	
17	17M	−	+	MVP	...	−	−	14.7/33.5	44	
18	17M	−	+	MVP	...	+S	+	7/24	29	
19	45M	+	+	...	...	+S	−	14.5/32.5	45	
20	43M	+	+	...	MVP	−	−	16/29	55	
21	54M	+	+	MVP	...	−	−	15/32.5	46	
22	51M	+	+	MVP	...	+S	−	12/29.5	41	
23	32M	+	+	MVP	...	+S	−	12/31	39	
24	72M	+	+	MVP	...	−	−	...	...	Severe scoliosis

*Not determined in Cases 13 and 24 because of severe scoliosis.

† These patients had clinical features of "straight back," but their condition did not fulfill the strict radiographic criteria.

− = absent; + = present; +M = marked; +S = slight.

Angio = angiocardiography; AP/Trans. = ratio of anteroposterior to transverse diameter of the chest as measured on chest X-ray film; Echo = echocardiography; MVP = mitral valve prolapse; Pectus = pectus excavatum; St. Back = "straight back."

transverse diameter ratio smaller than 2 standard deviations from the normal mean as reported by Twigg et al.[16] Echocardiograms, recorded in 21 patients, were reviewed for mitral valve prolapse, utilizing previously published criteria.[8] Left ventricular angiography was performed in the right anterior oblique projection in seven patients, and the description of prolapse of the mitral valve as discussed by Jeresaty[11] and Ranganathan et al.[12] was used to define this abnormality.

Results

All 24 patients had the characteristic auscultatory features of mitral valve prolapse—mid-late systolic click or late systolic apical murmur, or both—and the findings were confirmed by phonocardiography in 21 (Fig. 1). Echocardiographic confirmation was obtained in all 21 patients studied by this technique (Fig. 2). Prolapse of the mitral valve with mild to moderate mitral regurgitation was demonstrated by left ventricular angiography in all seven patients who underwent cardiac catheterization (Table I, Fig. 3).

Pectus excavatum (Fig. 2 and 3) was observed radiographically in 15 of 24 patients (62 percent). "Straight back" (Fig. 1) was present in four patients (17 percent). Two additional patients (8 percent) had severe scoliosis. Three patients had a combination of two abnormalities. Six patients (25 percent) had no definite chest deformity; two of these and a third patient with pectus excavatum had clinical features of "straight back," but their condition did not meet the strict radiographic criteria. Therefore, 18 of the 24 patients (75 percent) manifested a definite thoracic skeletal deformity and 2 had a probable deformity (Table II). The mean anteroposterior diameter of the chest and the mean anteroposterior transverse diameter ratio of these 24 patients were decreased as compared with normal standards (Table III), but the differences were not statistically significant.

Discussion

At least 75 percent of the patients in our series had skeletal thoracic deformities, thereby confirming the initial observations of DeLeon and Ronan,[14] who reported a similar prevalence rate of 78 percent. A more recent communication mentioned a lower though still significant prevalence rate of 47 percent.[15] We found pectus excavatum to be the most common deformity (62 percent) followed by "straight back" (17 percent) and scoliosis (8 percent). There

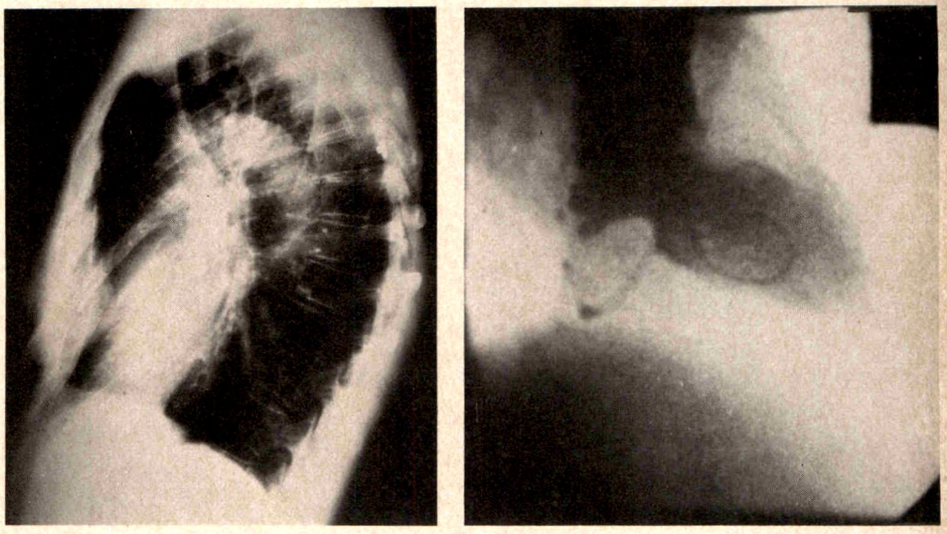


FIGURE 3. Case 4. **Left,** lateral chest X-ray film demonstrates marked pectus excavatum. **Right,** frame from the left ventricular angiogram shows the ventricle in late systole in the right anterior oblique view. The scalloped appearance of the mitral valve prolapsing into the left atrium is readily seen.

TABLE II

Prevalence of Thoracic Skeletal Abnormalities

	Patients					
	Females		Males		All Patients	
	no.	%	no.	%	no.	%
Total patients	14	100	10	100	24	100
Pectus excavatum	10	71	5	50	15	62
"Straight back"	2	14	2	20	4*	17
Scoliosis	1	7	1	10	2	8
Any deformity	12	86	6	60	18	75

* Three additional patients had clinical features of "straight back," but their condition did not meet the radiographic criteria.

TABLE III

Radiographic Diameters of the Thorax (mean ± 1 standard deviation)

	$\overline{AP}$ (cm)	AP/Trans (%)
Female subjects		
Present series	10.94 ± 2.26	40.61 ± 8.22
Normal*	11.96 ± 1.62	45.7 ± 6.67
	NS	NS
Male subjects		
Present series	12.64 ± 2.98	41.00 ± 8.39
Normal*	14.20 ± 1.69	47.0 ± 5.15
	NS	NS

* Normal standards as reported by Twigg et al.[16]

AP = mean anteroposterior diameter of the chest; AP/Trans = mean ratio of anteroposterior to transverse diameter of the chest; NS = no significant difference between data in present series and normal standards.

was no significant difference between the female and male patients.

Even though mitral valve prolapse occurs in patients with normal body build, it seems to be more frequently associated with asthenic habitus, pectus excavatum, "straight back" and, occasionally, kyphoscoliosis. These skeletal deformities may provide the easily identifiable clinical indicator that is necessary to arouse suspicion of mitral valve deformity and lead to more accurate definition of the disease.

These abnormalities are reminiscent of Marfan's syndrome, in which there is frequently prolapse of the mitral valve[17,18] as well as pectus excavatum and kyphoscoliosis.[19] Moreover, the mucoid degenerative changes described in patients with mitral valve prolapse and Marfan's syndrome are very similar.[6,7,20] One is tempted to postulate that the same mesenchymal heredity that determines the skeletal habitus also affects the mitral valve, resulting in weakening and stretching of the chordae tendineae, loss of leaflet support and eventual development of prolapse of the valve leaflets.

Patients with pectus excavatum or "straight back" occasionally manifest right ventricular hemodynamic restrictive phenomena,[21,22] probably as a result of "pancaking" of the heart within the shallow chest. Mechanical pressure on the heart could account for mitral valve distortion in only a small number of patients with an extremely shallow chest and is probably not a significant factor in the etiology of mitral valve prolapse.

Both "straight back" and pectus excavatum have been shown to be associated with "pseudoheart disease." The murmurs of the "straight back" syndrome are of basal and pulmonary location,[22] whereas in pectus excavatum murmurs can also be heard at the apex[21] and could be confused with those of mitral valve prolapse. Since these rather rare skeletal abnormalities are very prevalent in patients with prolapse of the mitral valve, patients should not be diagnosed as having "pseudoheart disease" until valve prolapse has been excluded.

Clinical implications: It is apparent that many patients (75 percent in our series) with mitral valve prolapse have easily recognizable chest wall and thoracic spine abnormalities that should alert the physician to consider mitral valve disease. Careful auscultation of the heart will almost invariably reveal the correct diagnosis, which can be substantiated by phonocardiography, echocardiography and, in selected cases, angiocardiography. The identification of these patients is extremely important since they tend to have potentially fatal ventricular arrhythmias[23–25] and are predisposed to bacterial endocarditis.[26,27]

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Termination of Ventricular Fibrillation in Dogs by Depolarizing a Critical Amount of Myocardium

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The role of a critical myocardial mass required to maintain ventricular fibrillation initiated by rapid ventricular pacing was studied by two methods in dogs placed on total cardiopulmonary bypass. In the first method, depolarization of a limited myocardial mass was accomplished by injecting potassium chloride into one or two coronary arteries. Injection of potassium chloride simultaneously into the left circumflex and left anterior descending coronary arteries abolished ventricular fibrillation more often than did injection into any other single or combination of two coronary arteries ($P < 0.0001$). Ventricular fibrillation could not be reinitiated as long as the left ventricle remained inexcitable. Immersing the heart in a solution of potassium chloride or injecting the solution into the right and left ventricular cavities failed to terminate ventricular fibrillation. The second method evaluated the amount of current necessary to terminate ventricular fibrillation when the current was passed between two right ventricular electrodes, between two left ventricular electrodes and between one right ventricular and one left ventricular electrode. Electrical shocks of equal magnitude terminated ventricular fibrillation most often when those shocks were delivered between an electrode located at the right ventricular apex and an electrode located at the posterior base of the left ventricle, and least often when the shock was delivered between two right ventricular electrodes. Successful defibrillation results when a critical amount of myocardium becomes depolarized by either potassium chloride or electrical discharge; depolarization of every cell in both ventricles is not necessary to terminate ventricular fibrillation in the entire heart.

Although the explanation for the pathogenesis of self-sustained fibrillation remains divided between the ectopic focus and reentry theories,[1–3] much evidence exists to substantiate the need for a critical myocardial mass to maintain self-sustained fibrillation. A critical mass represents the amount of myocardium that must be present and excitable for fibrillation to continue spontaneously. In the late 1800's, McWilliam[4] and Porter[5] noted that ventricular fibrillation was more easily supported in larger hearts and, in 1914, Garrey[6] demonstrated that when pieces of ventricular muscle with a surface area of less than 4 cm^2 were shaved from the wall of the fibrillating left ventricle, these pieces stopped fibrillating. The remaining portion of the ventricle continued to fibrillate until three fourths of the ventricular mass had been removed. In other experiments, after appropriate cuts divided the fibrillating heart into the right ventricle, interventricular septum and left ventricle, the right ventricle stopped fibrillating while fibrillation in the larger masses continued.

The purpose of this study was to test whether ventricular fibrillation can be terminated in the intact heart in situ by depolarizing only a limited population of cells. If ventricular fibrillation can be termi-

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nated in such a fashion, it indicates that the remaining excitable cells represent a critical mass that is insufficient to maintain self-supported ventricular fibrillation. Such a concept has been suggested to explain observations recorded during defibrillation studies in dogs using an intracavitary catheter electrode.[7] The results of our study provide direct proof in support of this concept.

Two types of experiments were devised. In one group of dogs we employed a solution of potassium chloride to depolarize a limited mass of myocardium by bolus injection of the solution into the right, left anterior descending or circumflex coronary artery. In the second group of dogs, we determined the amount of current and voltage necessary to terminate ventricular fibrillation in the entire heart when the current was passed in the form of a trapezoidal wave between two electrodes sewn on the right ventricle, between two electrodes sewn on the left ventricle and between various combinations of one right ventricular and one left ventricular electrode.

Methods

Healthy mongrel dogs of either sex weighing 15 to 30 kg were anesthetized with secobarbital (30 mg/kg body weight), intubated and ventilated with a Harvard respirator at a rate and tidal volume predicted from a nomogram. The chest was opened in the midline, and the pericardium was incised and retracted to cradle the heart.

Total cardiopulmonary bypass was achieved in both groups of animals. After ligation of the azygous vein and administration of heparin (3 mg/kg intravenously), large bore catheters to collect venous blood were inserted into the superior and inferior venae cavae through a right atriotomy and secured by purse-string sutures. Umbilical tapes, placed loosely around the venae cavae, were later tightened to direct all venous blood returning in the venae cavae into the venous catheters. Blood was also collected from a suction catheter placed in the chest cavity and from a left ventricular vent catheter and pumped (Sigma motor model T65, Leland Electric) into a filtered cardiotomy reservoir (model Q120, Bentley Laboratory) that emptied into the venous return line. Venous blood was drained by gravity into a disposable blood oxygenator (pediatric size Temptrol, model Q110, Bentley Laboratory), primed with saline and Ringer's lactate solution through which 100 percent oxygen was bubbled. The blood, warmed and oxygenated in the Temptrol oxygenator, was pumped by a finger pump (Sigma motor model TM1, Leland Electric) into a large arterial perfusion catheter that had been placed in the abdominal aorta by way of the femoral artery. Arterial flow rates were kept between 2 and 3 liters/min.

Systemic blood pressure was monitored on an oscilloscope by means of a strain gauge transducer (Statham 23BD) that was connected to an indwelling catheter placed in the carotid artery. Mean systolic blood pressure was maintained between 45 and 65 mm Hg by adjusting venous return, altering arterial flow rate or by infusing normal saline solution; vasopressors were not used. The body temperature of the dogs was kept between 98 and 101° F. Periodic blood gas and electrolyte determinations during the experiments revealed that partial pressure of oxygen was always greater than 100 mm Hg. Initial hypokalemia in some animals, possibly related to hyperventilation before institution of cardiopulmonary bypass, was gradually corrected. In the group of dogs that received intraarterial injections of potassium chloride, serum potassium concentrations slowly rose and reached levels of 5 to 7 mEq/liter by the end of the experiment. In the second group of animals, serum potassium levels gradually rose toward normal but rarely exceeded 4 mEq/liter. Plasma levels of sodium and chloride became elevated as a result of saline infusion. Arterial pH was kept above 7.25 with periodic infusion of sodium bicarbonate. The hematocrit level fell in most dogs as a result of blood loss, pump-induced hemolysis and dilution with saline infusion. However, the experimental results we obtained cannot be ascribed to metabolic or hematologic imbalances since comparisons were made between interventions performed in the same animal within limited time periods, during which abnormal metabolic or hematologic status would be expected to affect the entire heart more or less equally.

Electrical activity was recorded with bipolar J-shaped electrodes that were hooked into the epicardium of the right or left atrium, or both, and in the following epicardial ventricular sites: high right ventricle near the outflow tract, low right ventricle along the inferior border, posterobasal left ventricle, in the lateral free wall of the left ventricle adjacent to the interventricular septum, and apex of the left ventricle. The latter two left ventricular electrodes were placed to reflect distribution of the left anterior descending coronary artery, whereas the posterobasal electrode reflected distribution of the circumflex artery. Bipolar electrical activity was filtered between 40 and 500 hertz, displayed along with lead II of the electrocardiogram on a switched beam oscilloscope (DR8, Electronics for Medicine), and recorded on photographic paper at speeds of 50 and 100 mm/sec.

After the animal was placed on total cardiopulmonary bypass, we initiated ventricular fibrillation by rapidly stimulating either the right or left ventricle at rates of 20 to 100 times/sec for 5 to 30 seconds. Stimuli, obtained from a pulse generator through an isolation transformer (Digipulser, model 830; Isopulser, model 850, WP Instrument, Inc.), were rectangular pulses of 2 msec duration delivered over bipolar electrodes at an intensity of 1 1/2 to 2 times the diastolic threshold. In the potassium studies, stimuli of 30 volts and 5 milliamperes were sometimes used.

Ventricular fibrillation was considered present when totally disorganized ventricular activity continued spontaneously for a minimum of 15 to 30 seconds after cessation of ventricular stimulation. Ventricular fibrillation was considered terminated when either organized electrical activity or complete absence of all electrical activity replaced ventricular fibrillation for more than 5 seconds, simultaneously in all five of the epicardial ventricular leads and lead II.

Potassium Studies

In the initial group of eight dogs treated with potassium chloride infusion, polyethylene tubing (22 gauge, Deseret) was inserted by way of a small arteriotomy into the right coronary artery near its origin and into the midportion of the left anterior descending coronary artery. The tip of the tubing in the latter vessel was advanced in retrograde manner to the bifurcation of the main left coronary artery, where a single potassium chloride injection depolarized ventricular muscle located in areas perfused by both the circumflex and left anterior descending coronary arteries. Brief occlusion at the origin of the right coronary artery during retrograde infusion into the left anterior descending

artery prevented reflux of potassium chloride into the former vessel, so that the solution perfused primarily the left ventricle. If only the anterior or posterior left ventricular recording, but not both, was affected by the potassium chloride, the infusion was considered a single vessel infusion made into either the left anterior descending or circumflex coronary artery, respectively. In order to perfuse these vessels separately, in the final group of six animals subjected to potassium chloride infusion, the origins of the right, left anterior descending and circumflex coronary arteries were dissected free from the epicardium and each vessel was cannulated individually. The tips of the tubing, located within 1 to 2 cm of the origin of each coronary artery, were directed "downstream" and secured in place with epicardial or purse-string sutures. The small diameter of the polyethylene tubing allowed unimpeded coronary blood flow.

To determine whether depolarization of a limited myocardial mass could result in termination of ventricular fibrillation in the remaining myocardium, a fixed total amount of potassium chloride was injected into a single coronary artery, or equal portions of the total amount of potassium chloride were injected into two coronary arteries simultaneously. Thus, the distribution of the particular coronary artery or combination of coronary arteries perfused with potassium chloride determined the amount of myocardium that was depolarized. Although anastomoses between coronary arteries permitted a certain amount of cross circulation, the major portion of the ventricle not directly perfused remained unaffected by infusion of potassium chloride into the contralateral side, as judged by the epicardial recordings. In each experiment, we compared the efficacy of equal total amounts of potassium chloride in terminating fibrillation when the solution was injected into one or two coronary arteries.

Finally, in another group of animals, potassium chloride (25 to 50 ml, 1 mEq/ml) was injected into the cavity of the left or right ventricle, or both, or the entire heart in situ was immersed in a polyethylene "bag" filled with 160 ml of potassium chloride (1 mEq/ml) for 30 seconds.

Electrical Defibrillation Studies

In the group of 11 animals electrically shocked, pairs of circular electrodes (3.14 cm^2) were sewn on the right and left ventricular epicardium, in a plane parallel to the interventricular septum. The electrodes were cut from copper sheets and coated with a layer of solder; the copper did not come into direct contact with the myocardium. On the right ventricle, the electrodes were sewn close to the atrial border near the outflow tract (RV_{Base}, RV_B) and near the inferior margin of the right ventricular apex (RV_{Apex}, RV_A). On the left ventricle, they were sewn in the posterobasal area between the origins of the left anterior descending and circumflex coronary arteries (LV_{Base}, LV_B), and near the left ventricular apex (LV_{Apex}, LV_A). The current and voltage wave forms were recorded on a calibrated storage beam oscilloscope (Tektronix model D11) from which the amplitude was measured. All electrical grounds, including the right leg electrode for the electrocardiogram, were removed from the animal. The shock was delivered after ventricular fibrillation had been initiated and was present spontaneously for at least 30 seconds. We determined the current and voltage required to terminate ventricular fibrillation in the entire heart when the shock was delivered between the following pairs of electrode combinations: RV_B-RV_A, LV_B-LV_A, RV_B-LV_B, RV_A-LV_A, RV_B-LV_A and RV_A-LV_B. In addition, each electrode of each pair served as the "hot" electrode; that is, the current and voltage required to terminate fibrillation was determined separately for current flowing in each direction between two electrodes. The distance between each of the electrode pairs was measured and, at the conclusion of each experiment, the heart was removed and weighed.

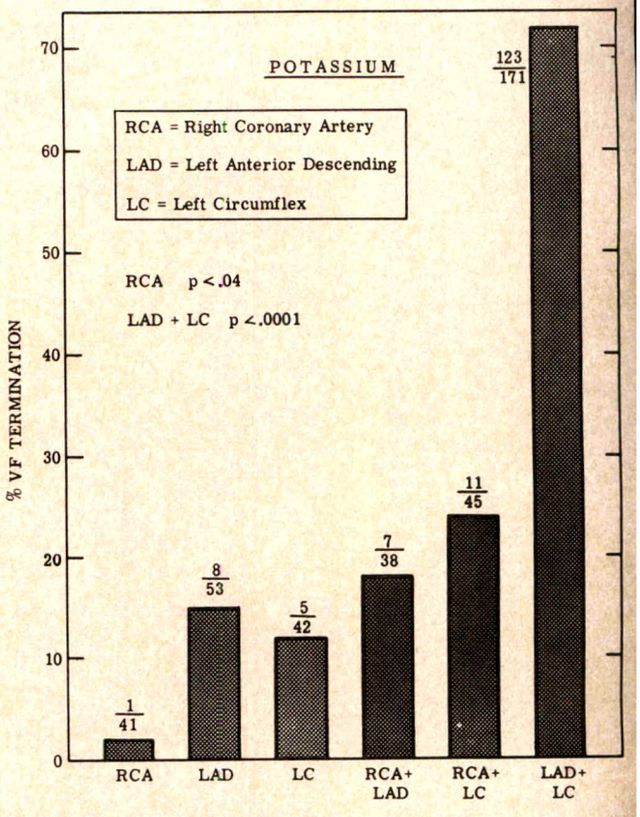

FIGURE 1. Graph indicating the percent of potassium chloride injections that successfully terminated ventricular fibrillation (Y axis) according to the single or combination of coronary arteries into which the solution was injected (X axis). Figures above the bars show the number of injections that terminated ventricular fibrillation (numerator) and the number of total injections (denominator). VF = ventricular fibrillation.

The electrical impulse used was a truncated exponential ("trapezoidal pulse") impulse delivered from a capacitor (800 μfarad at 600 volts direct current) that had been charged to a selected voltage with a variable regulated power supply. The length of the pulse (24 msec) was controlled by a variable integrated circuit timer that operated a silicon-controlled rectifier circuit.*

Results

Potassium Studies

The results from the entire group of 14 dogs were combined and are presented in Figure 1. Injections into the right coronary artery resulted in significantly fewer terminations than injections at any other site ($P < 0.04$), whereas the 72 percent rate of termination during simultaneous injection into the left anterior descending and circumflex coronary arteries was sig-

* The electrical circuitry was designed and built by Medical Electronics Consulting Associates, Indianapolis, Ind.

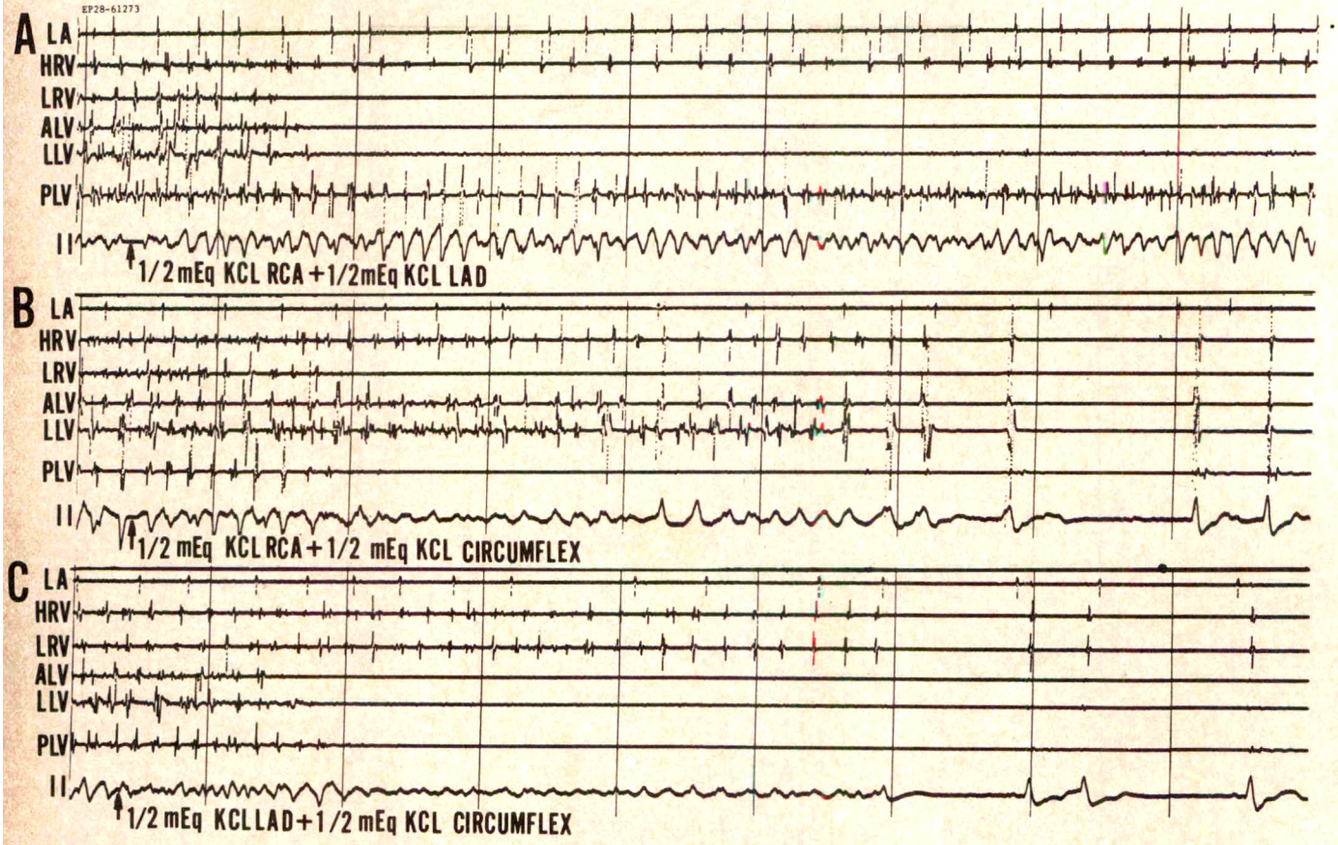

FIGURE 2. Termination of ventricular fibrillation by selective potassium chloride infusion. **A,** potassium chloride (1/2 mEq) injected simultaneously into both the right (RCA) and left anterior descending (LAD) coronary arteries at **arrow.** Electrical activity recorded at the LRV, ALV and LLV electrodes became suppressed. Ventricular fibrillation continued. **B,** potassium chloride injected simultaneously into both the right and circumflex coronary arteries. Electrical activity recorded at the LRV and PLV electrodes became suppressed. Ventricular fibrillation was terminated. **C,** potassium chloride injected simultaneously into both the left anterior and circumflex coronary arteries. Electrical activity recorded at the ALV, LLV and PLV electrodes became suppressed. Ventricular fibrillation terminated. LA = left atrium; HRV = high right ventricle near outflow tract; LRV = low right ventricle along the inferior border; ALV = apex of left ventricle reflecting distribution of left anterior descending artery; LLV = free wall of the lateral left ventricle adjacent to the interventricular septum, reflecting distribution of the left anterior descending artery; PLV = posterior left ventricle reflecting distribution of the circumflex coronary artery. II = lead II of the electrocardiogram. Time lines 1 second. Paper speed 50 mm/sec.

nificantly greater than terminations produced by any other injections ($P < 0.0001$). Simultaneous infusion of potassium chloride into the left anterior descending and circumflex coronary arteries naturally represents perfusion of the largest amount of ventricular myocardial mass. The success rate for defibrillation diminished in the other combinations, approximately in direct relation to the amount of ventricular myocardial mass perfused. Anastomotic circulation may have minimized these differences to a degree.

An example illustrating the termination of ventricular fibrillation by selective potassium chloride infusion is displayed in Figure 2. Potassium chloride injections (1 ml, 1 mEq/ml) into the right, left anterior descending or circumflex coronary artery, individually, depolarized limited portions of the ventricle supplied by these vessels but did not terminate ventricular fibrillation (not shown). Selective potassium chloride infusions terminated ventricular fibrillation within 5 to 6 seconds (Fig. 2, B and C) when the potassium chloride was injected simultaneously into either the right plus the circumflex coronary artery or the left anterior descending plus the circumflex coronary artery. Therefore, the remaining number of excitable cells represented a critical mass insufficient to maintain fibrillation. Infusion of potassium chloride into only one coronary artery or simultaneously into the right and left anterior descending coronary arteries failed to terminate ventricular fibrillation, presumably because the remaining excitable mass was large enough to support continued fibrillation. In this particular example, the high right ventricle and left atrium were not affected by infusions of potassium chloride into the right and circumflex coronary artery, respectively, because these areas were supplied by branches close to the origin of each coronary artery and were not perfused by the potassium chloride solution.

When ventricular fibrillation terminated after infusion of potassium chloride into the left coronary artery, the refractory period and diastolic stimulation threshold for the right ventricle remained at prefibrillation control values. However, rapid right ventricular stimulation failed to initiate ventricular fi-

brillation as long as the left ventricle remained depolarized by the effects of the potassium chloride (Fig. 3, A and B). After the return of left ventricular activity, fibrillation could be promptly restarted (Fig. 3C). Right ventricular inexcitability after infusion of potassium into the right coronary artery did not prevent precipitation of left ventricular fibrillation (not shown).

Ventricular fibrillation could not be terminated when potassium chloride (25 to 50 ml, 1 mEq/ml) was injected into the cavity of the right or left ventricle and confined there for 15 to 30 seconds. Similarly, ventricular fibrillation could not be terminated by immersing the entire heart into a plastic bag with a potassium chloride solution (160 ml, 1 mEq/ml) (not shown).

Electrical Defibrillation Studies

The combination of electrodes, the distance between electrodes and the heart weight were all major factors affecting the ability of the electroshock to defibrillate. The percent termination of ventricular fibrillation in 1,170 shocks for three current and voltage ranges is presented in Figure 4, in which each curve represents one of the electrode combinations. The rate of termination of ventricular fibrillation is significantly different among the six electrode combinations at each range for both voltage and amperes (overall P value <0.001 for each voltage and amperage range). Termination of ventricular fibrillation also occurred at less than 100 volts and less than 1.00 amperes, but the incidence was not large enough to analyze. The direction of current flow did not statistically influence the rate of termination.

Curves (Fig. 4) that decrease at 3.00 to 3.99 amperes and 300 to 399 volts can be explained by trials in which only one or two shocks were attempted at the lower two energy levels because the shocks failed to defibrillate the myocardium, and a large number of shocks—also unsuccessful—were attempted at the highest settings. This naturally reduced the percent of successful shocks at 3.00 to 3.99 amperes and 300 to 399 volts, while only minimally affecting the percentages at the lower two energy levels.

Heart weight was an important variable; it required significantly more volts (P <0.001) and amperes (P <0.001) to terminate ventricular fibrillation in heavier hearts, whether weights were analyzed for the right ventricle alone, the left ventricle alone (free wall of the left ventricle plus the interventricular septum) or total ventricular weight.

Increasing the distance between the LV_B and LV_A electrodes from 3 to 5 cm increased the rate of termination of ventricular fibrillation from 38.9 to 65 percent (P <0.05). However, increasing the distance between the RV_B and RV_A electrodes from 3 to 5 cm did not significantly increase the termination rate.

The relative importance of distance versus electrode combination could be assessed for two combinations by analyzing the data obtained with the RV_B-RV_A and LV_B-LV_A electrodes. In each experiment, the distance between RV_B and RV_A equaled the distance between LV_B and LV_A (3 to 5 cm). However, the LV_B-LV_A electrode combination yielded a higher percent of defibrillations for electroshocks of equal magnitude than did the RV_B-RV_A combination (P <0.001 except at 200 to 299 volts and 3.0 to 3.99 amperes). We conclude that, at least for these two electrode combinations, electrode position rather than interelectrode distance, was more important.

Subthreshold shocks were often followed by transient organization of recorded ventricular activity[7] but, presumably because an insufficient amount of myocardium was depolarized, fibrillation continued (Fig. 5A). Threshold shocks sometimes evoked short bursts of repetitive ventricular discharge (Fig. 5B) but were most often followed by abrupt termination of fibrillation.

Discussion

Critical ventricular mass required to maintain ventricular fibrillation: The data from the potassium infusion studies clearly establish for the intact dog heart in situ the importance of a critical ventricular mass to maintain self-supported ventricular fibrillation, which was initiated by rapid electrical stimulation. Ventricular fibrillation was terminated when potassium infusion reduced the remaining amount of excitable myocardium to a value less than that of the critical mass. Therefore, depolarization of every cell in both ventricles is not necessary to terminate ventricular fibrillation in the entire heart. The amount of this critical mass cannot be accurately quantified from our protocol, since we did not correlate combinations of potassium chloride injections that terminated fibrillation with the exact amount of myocardial mass perfused. This might be accomplished by injecting different dye markers into the right, left anterior descending and circumflex coronary arteries after completion of the potassium infusions. However, if we assume from Figure 1 that the entire left ventricle and interventricular septum, or a comparable amount of myocardium, must be depolarized to reduce the remaining excitable myocardium to a value insufficient to maintain ventricular fibrillation, then the critical mass necessary for ventricular fibrillation to continue in 13 dogs studied represents 28 percent of the total ventricular myocardium, a percentage remarkably similar to that found by Garrey.[6] This value is at best only an estimate for the dog heart because of the problems generated by cross circulation, our inability to perfuse branches arising very close to the origin of the coronary artery, and the fact the potassium chloride very probably did not uniformly depolarize the entire ventricular mass with which it made contact. This percentage may not necessarily be extrapolated directly to the patient with heart disease because the tendency to perpetuate fibrillation in the latter situation might be affected by many variables.

Support of concept of critical myocardial mass: The data from the electroshock studies provide indi-

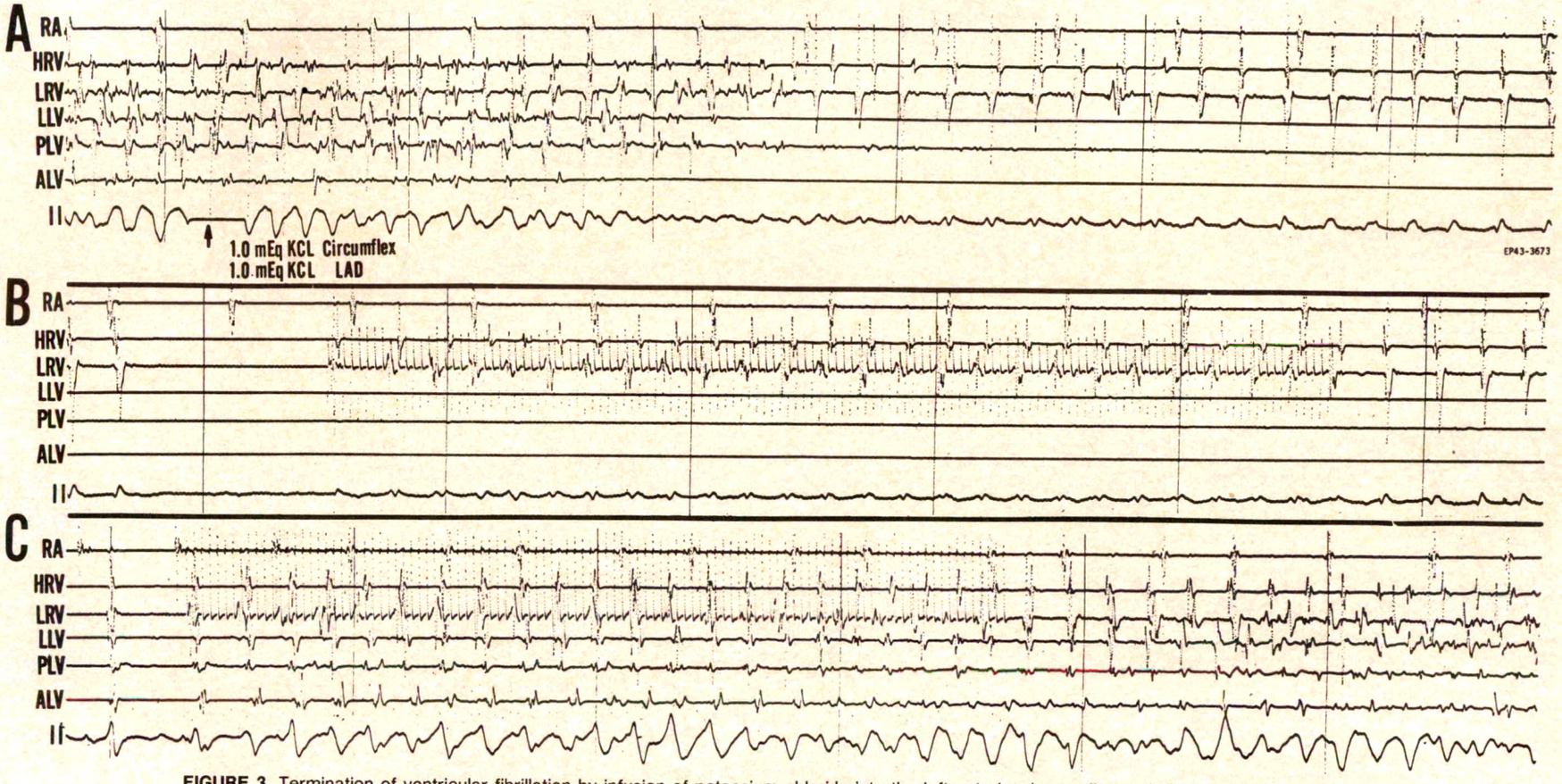

FIGURE 3. Termination of ventricular fibrillation by infusion of potassium chloride into the left anterior descending and circumflex arteries with failure to initiate ventricular fibrillation while the left ventricle remained inexcitable. Panels **A** and **B** are a continuous recording with the terminal two complexes in panel **A** repeated as the first two complexes in panel **B**. Potassium chloride (1 mEq/ml, 1 ml) was injected simultaneously into the left anterior descending and circumflex coronary arteries at **arrow.** Electrical activity recorded at the LLV, PLV and ALV electrodes became suppressed and an organized ventricular rhythm replaced ventricular fibrillation in the right ventricle. **B,** rapid right ventricular pacing (30/sec for about 4 seconds) failed to initiate ventricular fibrillation. **C,** after recovery of left ventricular excitability, right ventricular pacing (30/sec for about 3 1/2 seconds) promptly initiated ventricular fibrillation. RA = right atrium; other abbreviations as in Figure 2. Time lines 1 second. Paper speed 100 mm/sec.

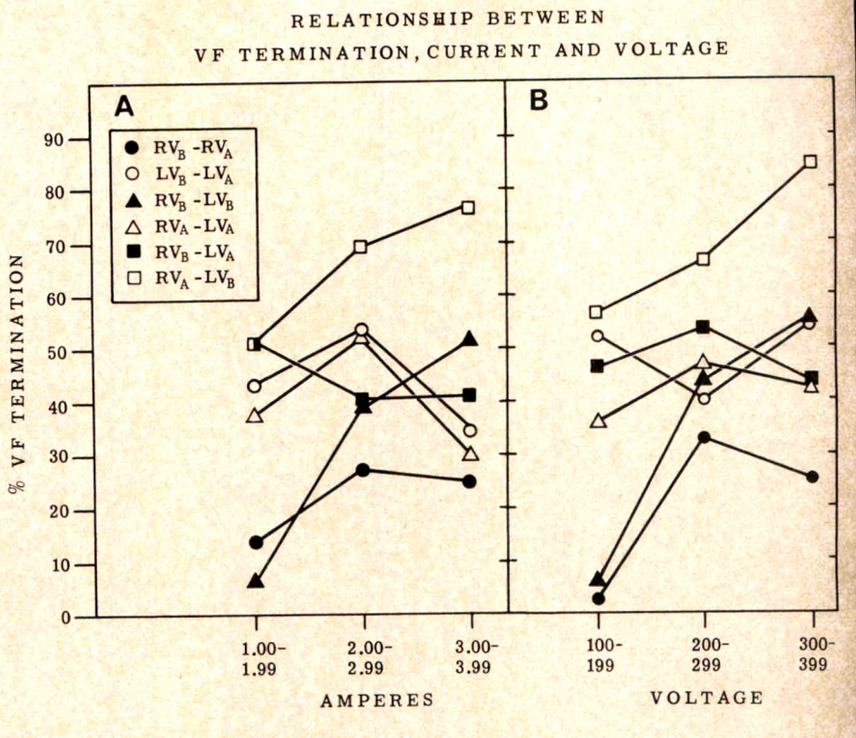

FIGURE 4. Percent of electroshocks that successfully terminated ventricular fibrillation (Y axis) for three voltage and current ranges (X axis), according to the electrode combination used. **A,** amperes; **B,** voltage. VF = ventricular fibrillation.

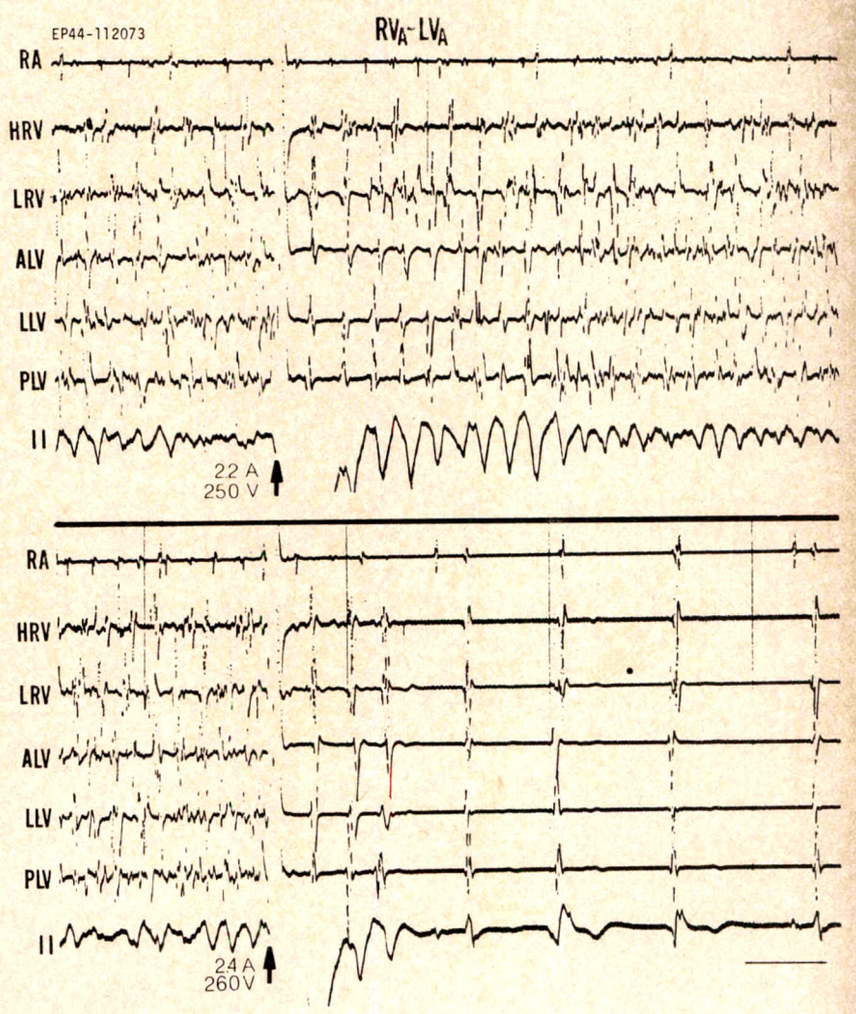

FIGURE 5. Electroshock termination of ventricular fibrillation with electrode combination RV_A-LV_A (right and left ventricular apex). **Top tracings,** subthreshold shock **(arrow)** caused transient regularization of recorded ventricular activity but ventricular fibrillation continued. **Bottom tracings,** threshold shock **(arrow)** terminated ventricular fibrillation after a brief burst of repetitive ventricular activity. Atrial fibrillation was also terminated. Paper speed 50 mm/sec. Horizontal line = 200 msec. A = amperes; V = volts; other abbreviations as in Figure 2.

rect evidence supporting the concept of a critical myocardial mass. Those data indicate that electrical shocks of equal magnitude terminated ventricular fibrillation most often when the shocks were delivered between the RV_A-LV_B electrodes and least often when they were delivered between the RV_B-RV_A electrodes. LV_B-LV_A and the remaining electrode combinations resulted in intermediate values. If these observations are explained in terms of the critical myocardial mass concept, then we would postulate that current flowing between two right ventricular electrodes (RV_B-RV_A) encountered, and therefore depolarized, the least number of cells, and resulted in the lowest rate of cardioversions. Current traveling between the right ventricular apex and posterobasal left ventricle (RV_A-LV_B) encountered, and therefore depolarized, the largest number of cells and resulted in the highest rate of cardioversions. Differences between the remaining electrode combinations may have been less great in terms of mass bounded by the two electrodes and resulted in intermediate values with a fair amount of overlap.

Distance between electrodes played a role in terminating fibrillation because interelectrode distance influenced the amount of mass through which the current flowed. However, the electrode combination seemed more important. The distance between RV_B-RV_A and LV_B-LV_A was equal in each experiment. Nevertheless, a higher percentage of terminations occurred with the LV_B-LV_A combination, presumably because of the larger mass bounded by the two left ventricular electrodes. The RV_A-LV_B electrode combination most successfully terminated ventricular fibrillation for two reasons. First, the combination spanned virtually the entire left ventricle and, second, its interelectrode distance was generally the largest.

Clinical implications: Speculations about the events that occur during clinical direct-current electroshock are consistent with the concepts advanced in this report. For example, during electrical defibrillation, the shock cannot discharge many cells that have just been depolarized spontaneously (by the fibrillating rhythm) and are absolutely refractory at the moment the shock is delivered. These cells naturally repolarize in advance of cells that are discharged at a slightly later time by electroshock, but, during a successful cardioversion, they represent a mass of cells insufficient to perpetuate the fibrillation. Continued fibrillation indicates failure to depolarize a sufficient number of cells. Administering a continuous series of shocks has been suggested to terminate refractory ventricular fibrillation.[8,9] It is possible that each successive shock depolarizes more muscle mass until finally a sufficient amount of myocardium becomes depolarized and fibrillation stops. Heart weight also has been important during defibrillated studies performed in man. The heavier the heart, the greater the energy required for defibrillation.[10]

This concept of critical mass may also explain the success of intracavitary catheter defibrillation in man and animals,[7,10] because depolarization of the entire heart is not necessary to terminate fibrillation. From our data, however, we would predict that energy requirements for defibrillation with a catheter electrode in or behind (coronary sinus) the left ventricle might be less than for a catheter electrode in the right ventricle. Such comparisons have not been performed by Mirowski and Mower.[12]

Acknowledgment

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Influence of Sympathetic Tone on Ventricular Fibrillation Threshold During Experimental Coronary Occlusion

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The effects of increased and decreased cardiac sympathetic tone and coronary occlusion on ventricular fibrillation threshold were determined in 14 open chest dogs anesthetized with sodium pentobarbital. Heart rate was kept constant by pacing the right atrium at cycle lengths of 500 msec. Ventricular fibrillation threshold was measured by delivering 350 msec trains of constant current stimuli with a frequency of 100 hertz and 2 msec duration. The minimal current of the train that induced fibrillation was taken as the ventricular fibrillation threshold. In seven animals, the effects of stellate stimulation were studied. Ventricular fibrillation threshold was measured during control periods, after 2 minutes of coronary occlusion, after 2 minutes of stellate stimulation and after 2 minutes of stellate stimulation and coronary occlusion. Coronary occlusion alone decreased ventricular fibrillation threshold an average of 35 percent of control values and stellate stimulation alone decreased the threshold an average of 42 percent of control values. The combination of both these interventions decreased ventricular fibrillation threshold an average of 63 percent of control values.

The effects of stellate ablation were studied in seven animals. Ventricular fibrillation threshold was measured during control periods, and during coronary occlusion before and after stellate ganglionectomy. Stellectomy increased the threshold an average of 31 percent above control values. After stellectomy, coronary occlusion decreased ventricular fibrillation threshold by only 11 percent of control values, a value 26 percent higher than the threshold during coronary occlusion before stellectomy. These findings may have therapeutic implications for the management of arrhythmias in patients with acute myocardial infarction or some forms of central nervous system disease.

The high mortality rate during the early phases of acute myocar infarction is mainly due to the high incidence of ventricular arrhy mias during this period. The mechanism of these arrhythmias has been completely defined; they may be due to enhanced automatic a reentrant mechanism, or both. Whatever the mechanism of th arrhythmias, many investigators have demonstrated that manipu tion of autonomic tone during experimental coronary occlusion in ences their incidence and severity.[1–10] In previous studies heart r has not been controlled, and it is therefore difficult to tell if the sults are due to the difference in heart rate before and after mani lation of autonomic tone or to the level of autonomic tone itself addition, previous studies have been concerned with the incidenc arrhythmias rather than with a quantitative measure of vulnerab to fibrillation independent of its initiating mechanism.

This study was conducted to determine the influence of ca sympathetic stimulation or surgical removal of the stellate and thoracic ganglia on fibrillation threshold during acute coronary

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* This work was done during the tenure of an Established Investigatorship of the American Heart Association.

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sion. Heart rate was controlled, and fibrillation threshold was determined in dogs in a control state, during coronary occlusion, during stellate stimulation, during coronary occlusion and stellate ganglion stimulation, after surgical removal of the stellates and upper thoracic ganglia and during coronary occlusion after ganglionectomy.

Methods

Experiments were performed in 14 mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg body weight) and ventilated with a fixed volume pump respirator. The chest was opened with a sternal splitting incision and the heart suspended in a pericardial cradle. The vagi were divided in the neck. The sinus node was crushed, a bipolar electrode placed on the right atrial appendage, and the heart paced at cycle lengths of 500 msec. The left anterior descending coronary artery or one of its major branches was isolated. Umbilical tape was passed around the artery and subsequently used to occlude it temporarily. A vertical lead body surface electrocardiogram and a bipolar electrogram from the lateral surface of the right ventricle were recorded.

To measure fibrillation threshold, 350 msec trains of constant current stimuli with a frequency of 100 hertz and a duration of 2 msec were delivered to the ventricle after every ninth basic driving cycle. The timing of the train with respect to a body surface electrocardiogram and a right ventricular electrogram are shown in Figure 1. In panel A the train stimulus intensity is subthreshold, and in panel B the intensity has been increased sufficiently so that it produces one propagated ventricular response. The trains of stimuli were delivered to two stainless steel hook electrodes. The anode was placed on the surface of the right ventricle in the region of the pulmonary conus, and the cathode was placed on the left ventricle near the border of the area that became cyanotic during temporary occlusion. The intensity of the train was increased in 0.5 milliampere increments until fibrillation was induced. The animals were defibrillated within 10 seconds of the onset of fibrillation, and repeat measurements were not made for 5 to 10 minutes after defibrillation.

Fibrillation threshold was measured in a control state, within 2 to 5 minutes of acute coronary occlusion and during alteration of sympathetic tone before and during coronary occlusion. The occlusion of the coronary artery was released as soon as fibrillation threshold was measured. In one dog repeated measurements of fibrillation threshold were made during control states and after 2 minutes of coronary occlusion. This was done to establish the reproducibility of the method. In another animal, the effects of both stellate stimulation and stellectomy on fibrillation threshold before and during coronary occlusion were determined.

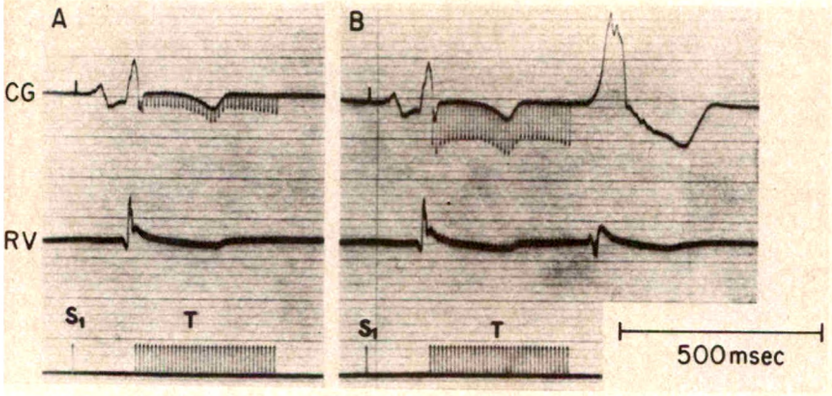

FIGURE 1. Vertical lead body surface electrocardiogram (ECG), a right ventricular (RV) electrogram, and stimulus pulses of the basic drive (S_1) and of the train (T) used to induce ventricular fibrillation. In **A** the intensity of the train is subthreshold and it does not induce a ventricular response. In **B** the intensity of the train has been increased sufficiently to induce one ventricular response.

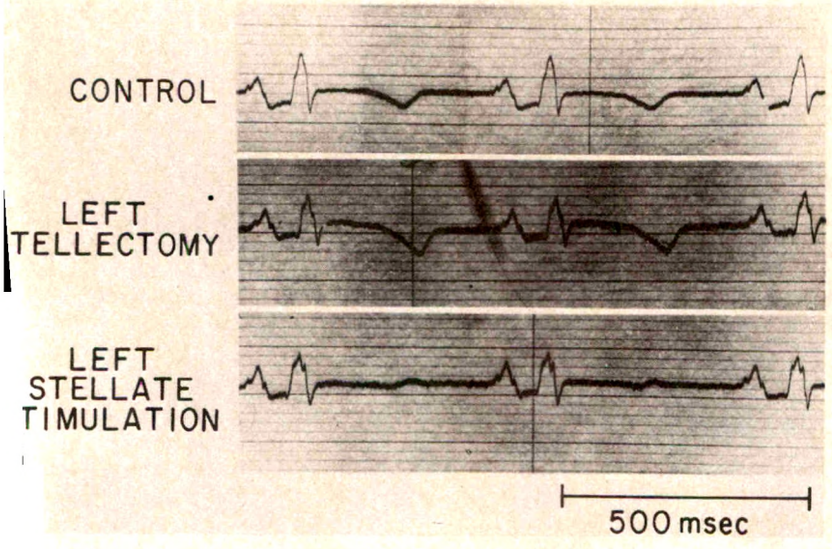

FIGURE 2. Vertical lead electrocardiograms of a dog taken during a control period **(top tracing)**, after left stellectomy **(middle tracing)** and during stimulation of the distal ends of the ansae subclaviae **(bottom tracing).**

The results from this animal are included with the results from animals in which only the effects of stimulation or stellate ablation were studied. The effects of sympathetic stimulation were studied in six additional dogs. In these animals the left stellate ganglion or the left dorsal and ventral ansae were isolated and stimulated with trains of pulses with a frequency of 12 hertz, a duration of 4 msec and an intensity of 5 to 16 volts. Change in T wave form in a vertical lead body surface electrocardiogram was taken as evidence of change in sympathetic tone. The effects of left stellate stimulation and removal on one dog's electrocardiogram are shown in Figure 2. Stimulation of the stellate ganglia was started 2 minutes before measurement of fibrillation threshold and continued during coronary occlusion. Measurements of threshold during sympathetic stimulation alone were alternated with measurements of sympathetic stimulation during coronary occlusion. In each animal 3 to 5 measurements were made under each condition. In six other dogs, the effects of sympathetic ablation were studied. Fibrillation thresholds were determined during a control state and after 2 minutes of coronary occlusion. Either the left stellate ganglion (two dogs) or both the left and right stellate ganglia (four dogs) were then excised together with the upper three or four thoracic ganglia. After ganglionectomy, 30 minutes was allowed to elapse and fibrillation threshold measurements with coronary occlusion were alternated with measurements without occlusion. In each animal two to five measurements were made under each of the two conditions.

Results

The ranges of time required to measure fibrillation threshold after 2 minutes of coronary occlusion alone were almost identical to those required to measure fibrillation threshold after 2 minutes of coronary occlusion in animals with stellate stimulation or stellectomy. With coronary occlusion alone, measurement of fibrillation threshold was started 2 minutes after occlusion of the artery and was completed an average of 82 ± 39 (standard deviation) seconds later. With stellate stimulation and coronary occlusion, measurement of fibrillation threshold was started 2 minutes after occlusion and the onset of stimulation and completed an average of 78 ± 47 seconds later. With stellectomy and coronary occlusion, measurement of fibrillation threshold was started 2 minutes after occlusion and completed an average of 82 ± 40 seconds later. Spontaneous arrhythmias rarely occurred and, if they did, a smaller vessel was occluded. If spontaneous arrhythmias persisted, the animal was excluded from the study. Fibrillation after release of the coronary artery did not occur in the animals studied.

Figure 3 is a bar graph of repeated measurements of fibrillation threshold made in one dog during control periods and after 2 minutes of coronary occlusion. In this animal, fibrillation threshold averaged 7 ± 1 (standard deviation) milliamperes in the control periods and 4 ± 1 milliamperes during coronary occlusion. Although the threshold in the control periods ranged from 6 to 9 milliamperes, there was no overlap in measurements made in control periods with those made during occlusion.

The effects of both stellate stimulation and stellectomy on fibrillation threshold before and during coronary occlusion usually could not be determined in the same animals because of the time required to complete all measurements. The determination of the effects of all these interventions in the same animal was successfully carried out in one dog (Fig. 4). One hour after left stellectomy alone, fibrillation threshold increased. After stellectomy, threshold decreased less during coronary occlusion than it had be-

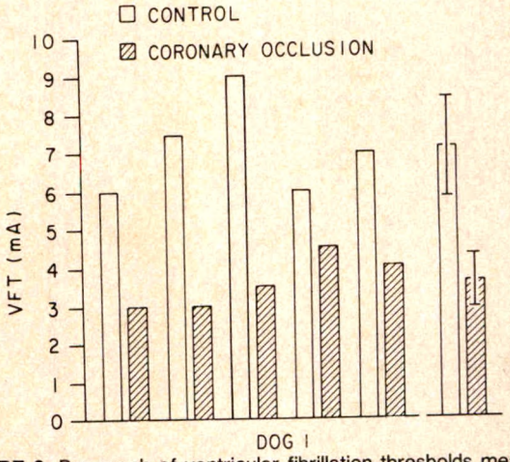

FIGURE 3. Bar graph of ventricular fibrillation thresholds measured during five control periods and five periods of temporary coronary occlusion. Fibrillation threshold is shown in milliamperes (mA). The last two bars on the graph show the averages and standard deviations of the control and coronary occlusion thresholds. VFT = ventricular fibrillation threshold.

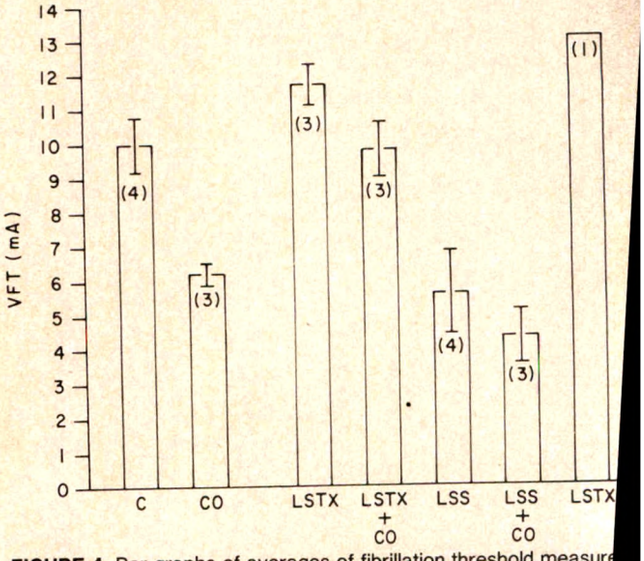

FIGURE 4. Bar graphs of averages of fibrillation threshold measure in milliamperes of one dog during control periods (C), during temp rary coronary occlusion (CO), after left stellectomy (LSTX), duri coronary occlusion after stellectomy, during stimulation of the dis ends of the left stellate (LSS) and during coronary occlusion and l stellate stimulation. The numbers in parentheses indicate the numb of measurements included in the averages. VFT = ventricular fib lation threshold.

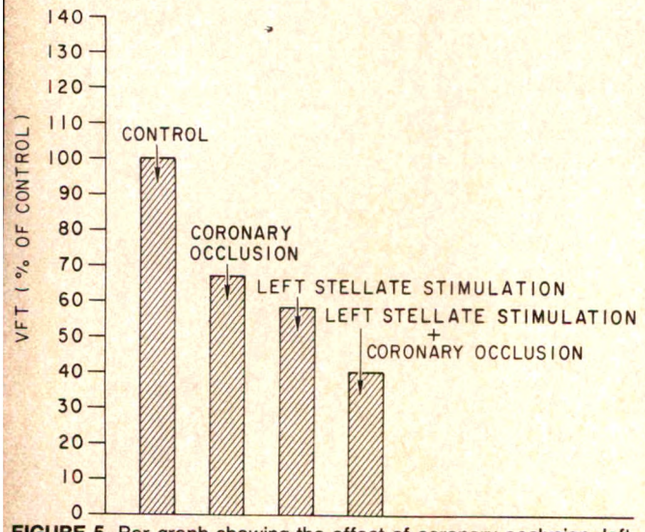

FIGURE 5. Bar graph showing the effect of coronary occlusion, left stellate stimulation and left stellate stimulation and coronary occlusion on fibrillation threshold. Fibrillation threshold is expressed as a percent of control level, and the graph is compiled from the average findings in seven dogs. VFT = ventricular fibrillation threshold.

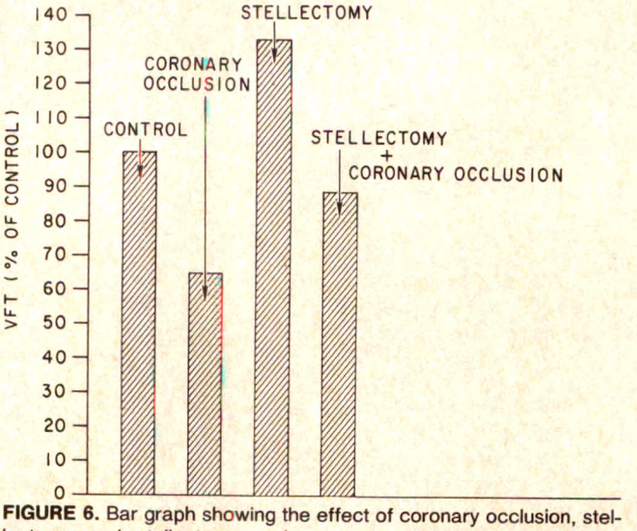

FIGURE 6. Bar graph showing the effect of coronary occlusion, stellectomy and stellectomy and coronary occlusion on fibrillation threshold. Fibrillation threshold is expressed as a percent of control level, and the graph is compiled from the average findings in seven dogs. VFT = ventricular fibrillation threshold.

fore stellectomy. Stimulation of the distal ansae subclaviae decreased fibrillation threshold more than coronary occlusion alone, and there was a further decrease in the threshold when the coronary artery was occluded during stellate stimulation. After these measurements were made, 1 hour was allowed to elapse and threshold was again measured. This measurement is shown as the last bar on the graph and is only 1 milliampere higher than the measurements of fibrillation threshold made 1 hour after stellectomy. This indicates that the preparation was stable. The results from this dog are included in the results of experiments in animals in which only the effects of stellate stimulation or stellectomy were studied.

Sympathetic stimulation and coronary occlusion: The effect of sympathetic stimulation on fibrillation threshold before and during coronary occlusion was studied in seven dogs, and the results of these experiments are summarized in Figure 5. In these animals, after coronary occlusion alone, fibrillation threshold decreased by an average of 35 percent from control values. Stimulation of the left stellate ganglion alone decreased fibrillation threshold by an average of 42 percent from control values. This decrease was comparable to that seen with coronary occlusion alone. The combination of sympathetic stimulation and coronary occlusion produced a further decrease in fibrillation threshold. With the combination of these two interventions, threshold to fibrillation fell by an average of 63 percent of control values, a level 27 percent lower than the threshold with coronary occlusion alone.

Stellectomy and coronary occlusion: The effect of stellectomy on fibrillation threshold before and during coronary occlusion was studied in seven dogs (Fig. 6). In these dogs, before stellectomy, coronary occlusion decreased fibrillation threshold by an average of 37 percent from control values. Stellectomy alone increased fibrillation threshold to an average of 31 percent above control values. After stellectomy, coronary occlusion decreased fibrillation threshold but, when compared with levels before stellectomy, threshold was decreased by an average of only 11 percent from control levels, a level 26 percent higher than fibrillation threshold during coronary occlusion before stellectomy.

Discussion

As early as 1936 the study of Cox and Robertson[1] implicated an increase in sympathetic tone as a contributory factor in the occurrence of arrhythmias after coronary occlusion; they observed a lower mortality rate in dogs with acute coronary occlusion and prior ganglionectomy than in dogs with intact cardiac sympathetic nerves. Similar findings have been reported by others.[2–5]

The study of Schaal et al.[5] was performed in unanesthetized dogs with chronic cardiac denervation. Maling and Moran[6] demonstrated an increased incidence of arrhythmias in unanesthetized dogs with coronary occlusion during infusion of catecholamines, and Harris et al.[10] showed that stimulation of the cardiac sympathetic nerves in anesthetized dogs with coronary occlusion also increased ectopic ventricular activity. None of the previous studies measured fibrillation threshold and none controlled heart rate. The failure to control heart rate in previous studies makes interpretation of results difficult. Han et al.[11] reported that temporal dispersion of refractory periods was greater and fibrillation threshold lower with slow than with fast heart rates. More recently, how-

ever, Kent et al.[12] found that in the setting of acute coronary occlusion, fibrillation threshold is reduced by tachycardia.

Clinical implication: In our study, heart rate was maintained constant during all interventions and was therefore not a factor in the observed changes in vulnerability to fibrillation. Stimulation of the left stellate during acute coronary occlusion decreased fibrillation threshold more than either intervention alone, and stellectomy had a protective effect. The results of this study indicate that, in addition to the role the sympathetic nerves may have in the incidence of arrhythmias in the setting of coronary occlusion, increased levels of sympathetic tone may sometimes lead to lethal arrhythmias in patients with some forms of neurologic disease.

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Effect of Manganese Chloride and Verapamil on Automaticity of Digitalized Purkinje Fibers

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The effects of manganese chloride ($MnCl_2$) and verapamil on automaticity of digitalized Purkinje fibers were studied using conventional microelectrode techniques. The studies were made in isolated, spontaneously beating Purkinje preparations. Ouabain alone consistently increased the automatic rate, whereas no such increase was observed when the preparations were superfused with a mixture of ouabain and $MnCl_2$. $MnCl_2$ was also shown to be effective in suppressing the enhanced automaticity induced by ouabain. $MnCl_2$ alone did not have a significant effect on the spontaneous rate of Purkinje fibers. The effect of verapamil was similar to that of $MnCl_2$ in preventing and suppressing the ouabain-induced increase in automaticity. $MnCl_2$ and verapamil have been shown to inhibit the slow inward calcium current of cardiac fibers. The results therefore suggest that an inward calcium ion current may play a role in the development of digitalis-induced increase in the slope of phase 4 depolarization in Purkinje fibers.

Ventricular arrhythmias accompanying digitalis intoxication have usually been attributed to enhanced phase 4 depolarization of Purkinje fibers.[1,2] Recently, Ferrier and Moe[3] examined the effects of calcium ions and acetylstrophanthidin on canine Purkinje fibers and observed the development of transient depolarization after a series of driven responses. Such transient depolarization could occasionally reach threshold potentials and cause spontaneous responses. They suggested that the transient depolarization rather than "true" phase 4 depolarization is responsible for ventricular ectopic beats induced by digitalis. In their experiments the production of transient depolarizations could be prevented by the addition of manganese chloride to the perfusing Tyrode solution. Since $MnCl_2$ has been shown to block a slow inward calcium ion current associated with cardiac action potentials,[4–6] they concluded that the transient depolarization may be due to an influx of calcium ions.

Many ventricular ectopic beats resulting from digitalis intoxication are still believed to be due to an increase in the slope of "true" phase 4 depolarization of Purkinje fibers. This study was therefore undertaken to determine whether the ouabain-induced increase in the slope of phase 4 depolarization can also be prevented by manganese ions and verapamil. The enhanced automaticity could indeed be prevented by these agents, suggesting that an influx of calcium ion may also play a role in increasing the slope of phase 4 depolarization in digitalized Purkinje fibers.

Methods

Hearts were excised from dogs anesthetized with an intravenous injection of pentobarbital sodium, 30 mg/kg body weight. Papillary muscle with attached false tendon was dissected from the right or left ventricle and stored in oxygenated Tyrode solution. The preparation was then pinned under slight tension to a paraffin block in a tissue bath. Modified Tyrode solution

rom the Department of Medicine (Cardiology), lbany Medical College of Union University, and e Electrocardiography Laboratory, Albany edical Center Hospital, Albany, N. Y. This udy was supported by Contract NHLI-72-2974 m the National Institutes of Health, Bethesda, ., a grant from the Heart Association of East- New York, Albany, N. Y. and institutional nt GRS-FR-5394 from Albany Medical Col- e. Manuscript accepted November 20, 1974. Address for reprints: Jaok Han, MD, Department of Medicine, Albany Medical College, Albany, N. Y. 12208.

equilibrated in a reservoir with 95 percent oxygen and 5 percent carbon dioxide was infused into the bath at a rate of 5 ml/min. The temperature in the bath was maintained at 37° to 38° C and remained constant during any experiment. The composition of the Tyrode solution in millimoles was sodium chloride, 137; dextrose, 5.5; potassium chloride, 2.7; calcium chloride, 2.7; magnesium chloride, 0.5; sodium phosphate, 0.9; and sodium bicarbonate, 24.0. Transmembrane potentials of Purkinje fibers were recorded with conventional microelectrode techniques. Glass microelectrodes were filled with 2.7 molar potassium chloride, and the resistance of these electrodes ranged from 20 to 30 megohms. A silver wire indifferent electrode was in contact with the Tyrode solution in the bath. Action potentials were continuously monitored on an oscilloscope and photographed using a Grass camera. A series of Tektronix wave form and pulse generators were used to deliver pacing stimuli to a pair of bipolar electrodes attached to the preparation. Some of the preparations were driven by applying suprathreshold rectangular pulses at a cycle length of 630 msec.

Ouabain octahydrate was dissolved in 0.9 percent saline solution to make a stock solution in a concentration of 1 mg/ml. The working solution in a concentration of 2.0×10^{-7} M was prepared by diluting the stock solution with Tyrode solution. Manganese chloride ($MnCl_2$) and verapamil were dissolved in distilled water to make stock solutions of 4 and 1 mg/ml, respectively. The working solutions of $MnCl_2$ in a concentration of 4.0×10^{-4} M and verapamil in a concentration of 2.0×10^{-6} M were then prepared by diluting the stock solutions with the Tyrode solution. In this study, the effects of ouabain and $MnCl_2$ were analyzed from the results of those experiments in which the microelectrodes remained in the same cell throughout the experiment.

Results

Effect of Ouabain Alone

In these experiments only those preparations with a spontaneous rate of 15 to 75 beats/min were used. The effect of ouabain alone on the Purkinje fiber automaticity was first studied in seven preparations. Ouabain consistently increased the rate of spontaneous discharge in all seven preparations; the results of a typical experiment are depicted in Figure 1. Record A shows transmembrane potentials of a spontaneously beating Purkinje fiber at a rate of 18 beats/min. At the arrow labeled O, superfusion of the preparation with ouabain was begun. In records B to D, the rate increased steadily to 36, 72 and 140 beats/min at 15, 24 and 31 minutes, respectively, after the start of ouabain superfusion. The increase in automaticity was largely due to an increase in the slope of phase 4 depolarization. In four experiments the amplitude of the action potentials decreased with the increase in automaticity. In the remaining three experiments a biphasic change with an initial slight increase before the decrease in the action potential amplitude was observed. These variations were mainly due to corresponding changes in the maximal diastolic potential.

Effect of $MnCl_2$

Ouabain plus $MnCl_2$: The effect of $MnCl_2$ on the spontaneous rate of digitalized Purkinje fibers was studied with two different types of experimental design. In the first type of experiment, six preparations were superfused with Tyrode solution containing ouabain and $MnCl_2$ throughout the experiment. In all six preparations, a mild decrease in the spontaneous rate occurred in the presence of $MnCl_2$. The important observation was that no increase in the spontaneous rate was observed in these preparations in contrast to findings in preparations treated with ouabain alone. Figure 2 illustrates the results of one of these experiments. Record A shows transmembrane potentials of a spontaneously beating Purkinje fiber at a rate of 36 beats/min. At the arrow labeled O + MN, superfusion of the preparation with ouabain and $MnCl_2$ was begun. In record B, 15 minutes after the beginning of superfusion with the mixture, the spontaneous rate of the preparation decreased to 26 beats/min. In record C, 24 minutes after the start of superfusion, the spontaneous rate further slowed to 20 beats/min.

Ouabain followed by ouabain-$MnCl_2$ mixture: In the second type of experiment, four preparations were first superfused with ouabain until the sponta-

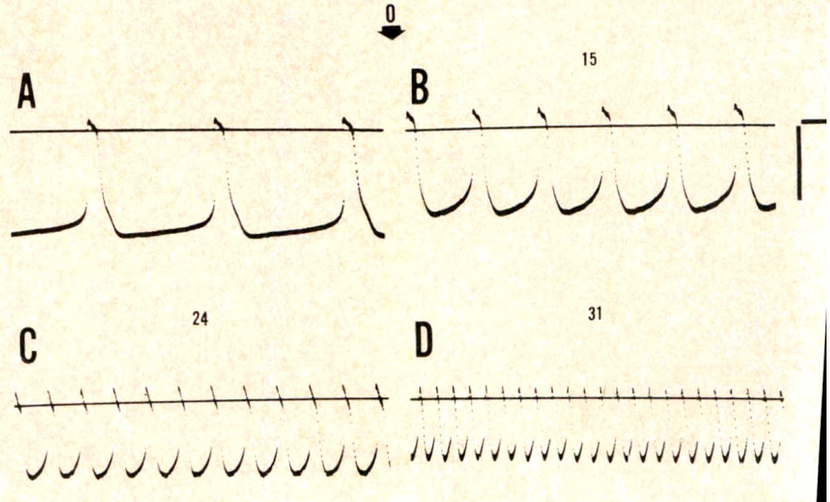

FIGURE 1. Effect of ouabain on the rate of a spontaneously beating Purkinje fiber. O = ouabain. The number at the top of each panel indicates the time in minutes after the beginning of superfusion of ouabain. Calibration: horizontal line = 1 second; vertical line = 50 mv. See text.

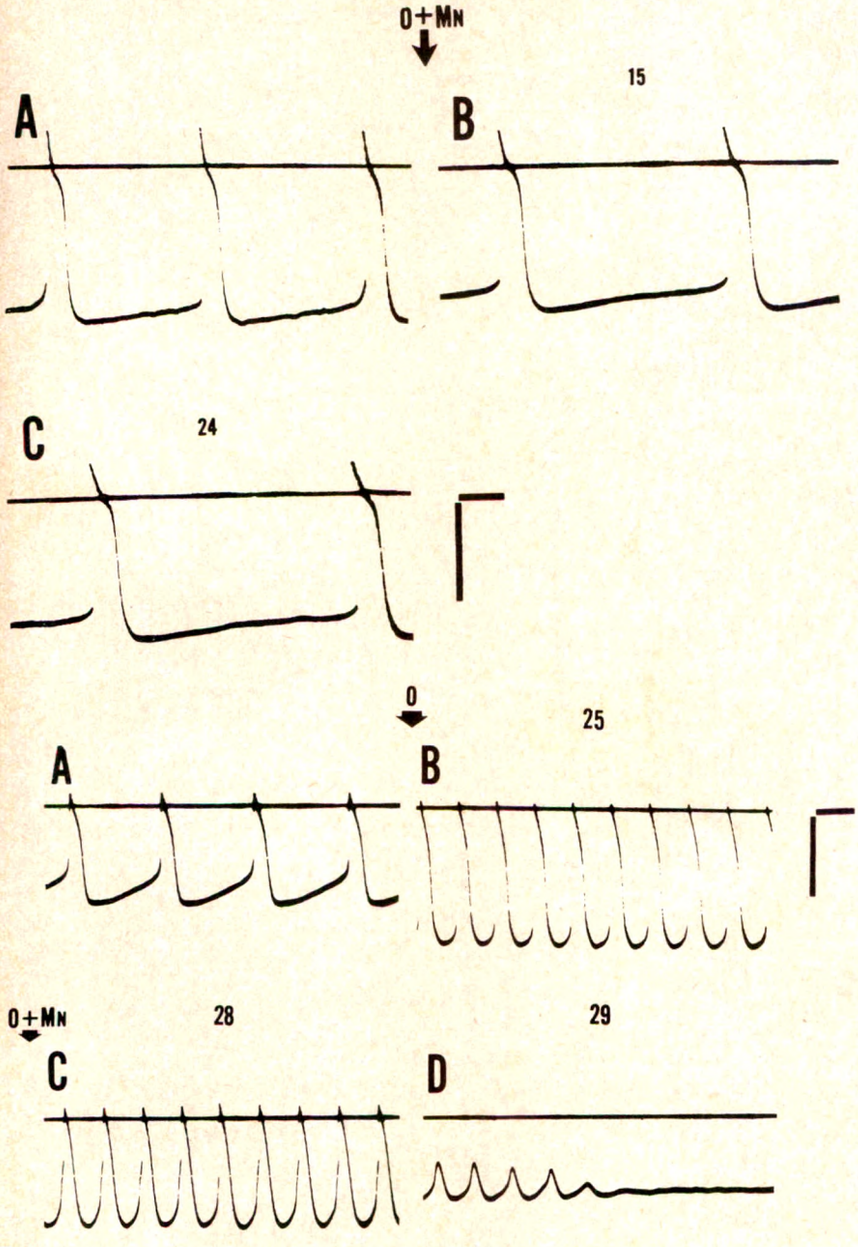

FIGURE 2. Effect of a mixture of ouabain and $MnCl_2$ on the spontaneous rate of a Purkinje fiber. O + MN = ouabain + $MnCl_2$. Other conventions as in Figure 1. Calibration: horizontal line = 500 msec; vertical line = 50 mv. See text.

FIGURE 3. Inhibitory effect of $MnCl_2$ on the ouabain-induced increase in automaticity of a Purkinje fiber. Conventions as in Figures 1 and 2. Calibration: horizontal line = 500 msec; vertical line = 50 mv. See text.

neous rate of the preparation was greatly increased, and the mixture of ouabain and $MnCl_2$ was then superfused to the preparation. Manganese chloride was able to reverse the increased automaticity induced by ouabain in all four experiments, and the results of one of these experiments are depicted in Figure 3. Record A shows transmembrane potentials of a spontaneously beating Purkinje fiber at a rate of 48 beats/min. At the arrow labeled O, ouabain was superfused to the preparation. In record B, 25 minutes after the beginning of ouabain superfusion, the spontaneous rate increased to 120 beats/min. At the arrow labeled O + MN, the mixture of ouabain and $MnCl_2$ was superfused to the preparation. In record C, 28 minutes after the beginning of ouabain superfusion and about 3 minutes after the start of superfusion with the mixture of ouabain and $MnCl_2$, a further increase in the spontaneous rate was interrupted and the rate actually began to decrease slightly. In record D, 1 minute later, the amplitude of the action potentials abruptly decreased, followed by cessation of the spontaneous activity.

$MnCl_2$ alone: In six experiments $MnCl_2$ alone was superfused to the preparations. The results of five experiments showed a mild decrease in the spontaneous rate 5 to 10 minutes after the beginning of the superfusion. Figure 4 illustrates the results of one of these experiments. Record A shows the transmembrane potentials of a spontaneously beating Purkinje fiber at a rate of 18 beats/min. At the arrow labeled MN, $MnCl_2$ was superfused to the preparation. As shown in records B and C, the spontaneous rate of

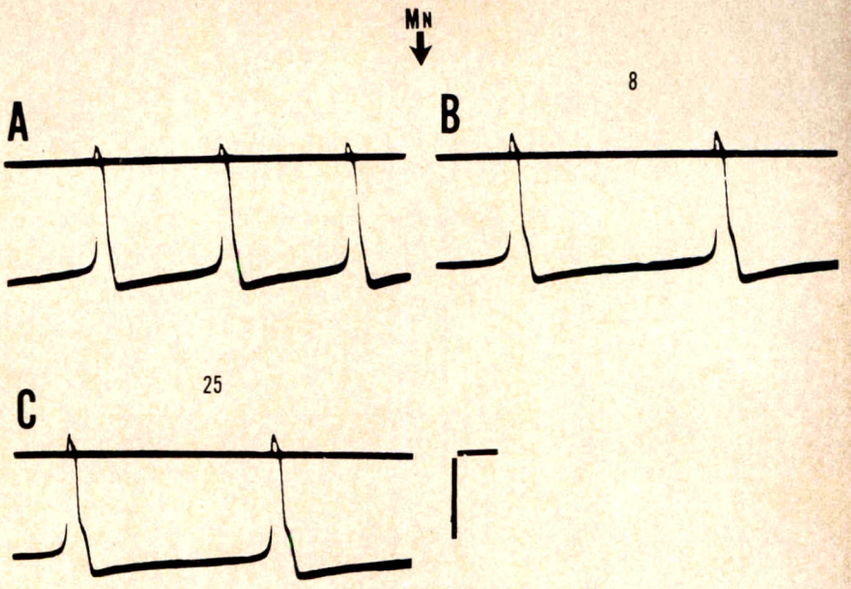

FIGURE 4. Effect of $MnCl_2$ alone on a spontaneously beating Purkinje fiber. MN = $MnCl_2$; other conventions as in Figure 1. Calibration: horizontal line = 1 second; vertical line = 50 mv. See text.

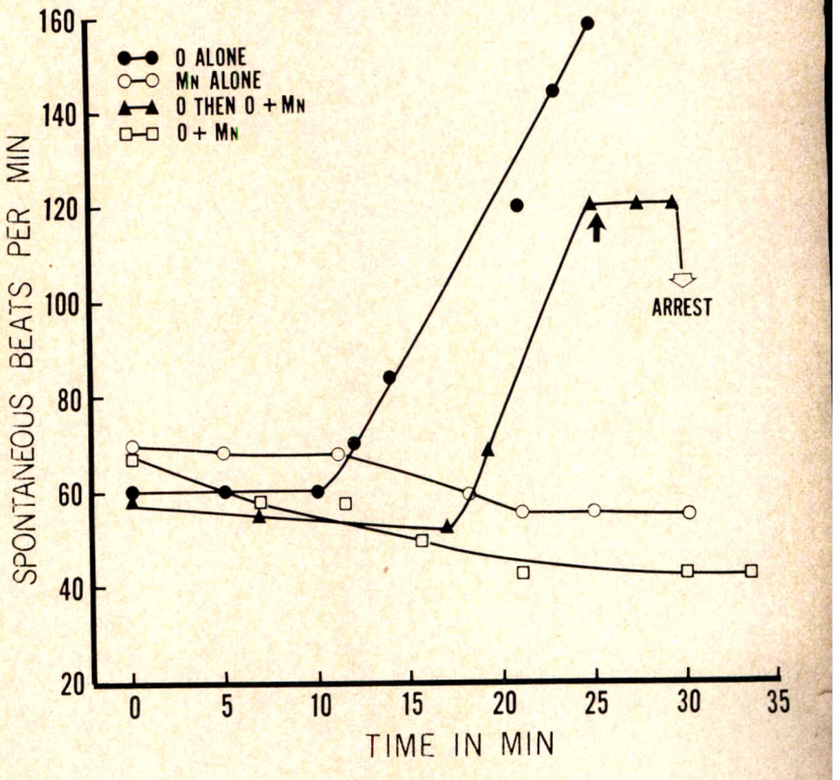

FIGURE 5. Comparison of various effects of $MnCl_2$ (MN) on the rate of spontaneously beating Purkinje fibers under different conditions. O = ouabain. See text.

the preparation then decreased slightly to 12 beats/min at 8 minutes and remained about the same for the remaining 25 minutes of the experiment. In the sixth experiment, a very slight increase in rate was observed during superfusion with $MnCl_2$ alone.

Figure 5 summarizes the effect of $MnCl_2$ on the spontaneous rates of Purkinje fibers under various conditions, presenting the results of a representative experiment of each of the four types. The Purkinje fiber preparation superfused with ouabain alone was characterized by a rapid and steady increase in the spontaneous rate beginning about 10 minutes after start of the ouabain superfusion. In the preparation superfused with both ouabain and $MnCl_2$, a mild decrease in the spontaneous rate was observed. In the experiment in which the spontaneous rate was first increased by ouabain, the addition of $MnCl_2$ (indicated by a solid arrow) prevented further increases in the rate, followed by arrest or cessation of spontaneous activity. The spontaneous rate of Purkinje tissue exposed to $MnCl_2$ alone showed no obvious change for the first 10 minutes and then decreased slightly.

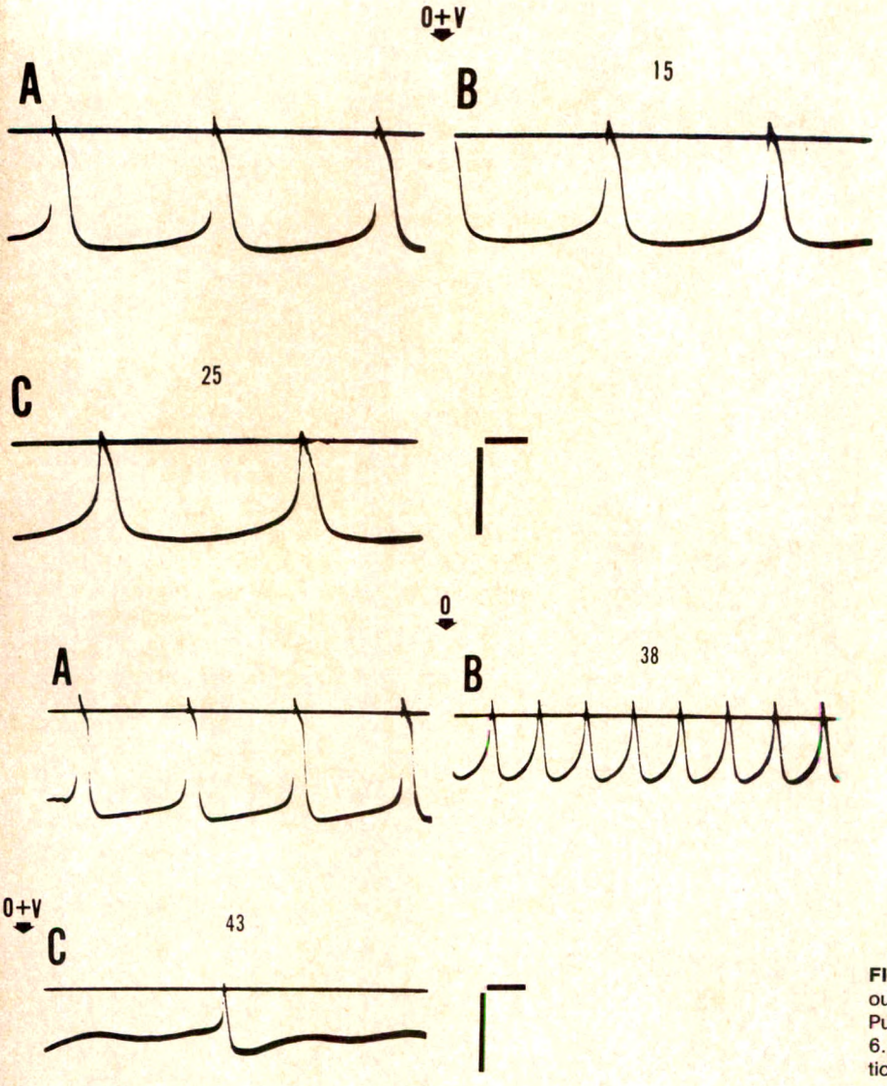

FIGURE 6. Effect of a mixture of ouabain and verapamil on the spontaneous rate of a Purkinje fiber. O + V = ouabain + verapamil. Other conventions as in Figure 1. Calibration: horizontal line = 500 msec; vertical line = 50 mv. See text.

FIGURE 7. Inhibitory effect of verapamil on the ouabain-induced increase in automaticity of a Purkinje fiber. Conventions as in Figures 1 and 6. Calibrations: horizontal line = 1 second; vertical line = 50 mv. See text.

Comparison of these results clearly indicates that $MnCl_2$ is effective in preventing the increase in automaticity of Purkinje fibers induced by ouabain.

Effect of Verapamil

The observed effect of $MnCl_2$ suggested that the increase in phase 4 depolarization induced by ouabain is related to an increase in calcium conductance. Since verapamil is also known to block a slow calcium current, some experiments were performed to test whether the effect of ouabain can be similarly prevented by verapamil.

The effect of verapamil on automaticity of digitalized Purkinje fibers was studied in six experiments in a manner similar to that of $MnCl_2$. All of these experiments demonstrated that verapamil, like $MnCl_2$, could prevent the enhanced automaticity induced by ouabain. Figure 6 shows the results of one of these experiments. Record A shows the control spontaneous rate of the preparation at about 36 beats/min. At the arrow labeled O + V, the preparation was superfused with a mixture of verapamil in a concentration of 2.0×10^{-6} M and ouabain in a concentration of 2.0×10^{-7} M. In the course of 25 minutes of superfusion, a slight decrease in the spontaneous rate (to about 24 beats/min) and the amplitude of the action potential was observed. In three other experiments, verapamil was also able to reverse a ouabain-induced increase in automaticity. Figure 7 shows the results of a representative experiment. Record A shows the control spontaneous rate of the preparation at about 24 beats/min. The preparation was first superfused with ouabain in a concentration of 2.0×10^{-7} M, and record B shows that the spontaneous rate increased to about 48 beats/min 38 minutes after the beginning of this superfusion. The preparation was then superfused with the mixture of ouabain and verapamil. In record C, about 5 minutes after this superfusion, the spontaneous rate decreased to about 10 beats/min.

Discussion

In this study, the effect of $MnCl_2$ on automaticity of digitalized Purkinje fibers was studied in spontaneously beating preparations. Ouabain alone consis-

tently enhanced the spontaneous rate to four or more times its control value. This increase was primarily due to an increase in the slope of phase 4 depolarization. These results are in accord with those obtained from earlier experiments by others[7,8] in intact dog hearts. When $MnCl_2$ was applied with ouabain to the preparation, the spontaneous rate was not generally altered except for a few preparations in which a slight decrease in the rate was observed. Manganese chloride was also effective in suppressing the increased spontaneous activity induced by ouabain. Verapamil was similarly effective in preventing and reversing the ouabain-induced increase in automaticity of the Purkinje tissue.

Manganese, verapamil and calcium currents: Ample evidence is available to support the view that manganese ions and verapamil inhibit the inward calcium current of cardiac cells.[4–6,9] Various studies with the voltage clamp technique[10–12] demonstrated that the slow inward current occurring during the plateau of cardiac action potentials is related to an influx of calcium ion. Manganese chloride and verapamil were shown to prevent such an inward current in cardiac fibers.[4–6,9] Our observations that $MnCl_2$ and verapamil prevent or reverse the ouabain-induced increase in automaticity suggest that the effect of ouabain on phase 4 depolarization is, in part, related to an influx of calcium ion. Manganese chloride alone had no appreciable effect on the automaticity of nondigitalized Purkinje fibers. This suggests that calcium conductance plays an insignificant role during phase 4 of normal Purkinje fibers. This is in keeping with the well accepted view that phase 4 depolarization of normal Purkinje fibers is primarily due to a progressive decrease in potassium conductance and a gradual increase in sodium conductance during diastole.[13,14]

Clinical implication: The slow calcium inward current that is present during the plateau of cardiac action potentials is speculated to be linked to the excitation-contraction coupling of cardiac fibers.[12,15] Therefore, an increase in calcium ion influx induced by digitalis in ventricular myocardial fibers could possibly manifest itself as positive inotropism, whereas in Purkinje fibers it could result in an increase in the slope of phase 4 depolarization and enhanced automaticity. The ability of $MnCl_2$ and verapamil to prevent the development of enhanced automaticity in digitalized Purkinje fibers may imply that they could be used as antiarrhythmic agents for digitalis-induced arrhythmias. However, their use in patients with digitalis toxicity may not be practical because they may inhibit the inward calcium current in myocardial fibers and decrease contractility of the ventricular myocardium.

Acknowledgment

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Use of a Balloon-Tipped Flotation Electrode Catheter for Cardiac Monitoring

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A new balloon-tipped flotation catheter equipped with two pairs of electrodes has been developed for simultaneous monitoring of cardiac rhythm and hemodynamics as well as for temporary emergency atrial, ventricular and atrioventricular sequential pacing. Experience in 43 patients demonstrates the following: (1) The catheter can be passed and positioned with the tip in the pulmonary artery or its branches at the bedside without the use of fluoroscopy as easily as the standard (Swan-Ganz) catheters. (2) With the catheter in the proper position and with the use of appropriate filters (proximal, 50 to 300 hertz; distal, 15 to 300 hertz), the intracavitary electrograms recorded from the proximal and distal pair of electrodes provide characteristic high right atrial and right ventricular signals, virtually free of noise artifact, baseline drift and respiratory variation, that are particularly suitable for automated on-line monitoring of cardiac rhythm. (3) When indicated, atrial, ventricular or atrioventricular sequential pacing can be initiated without delay. (4) Large artifact-free right ventricular intracavitary signals can be used for reliable and consistent operation of any device requiring QRS triggering mechanisms. (5) Monitoring of pulmonary arterial or pulmonary capillary wedge pressure and withdrawal of blood samples from the central circulation is possible. This device can be particularly useful in patients with hemodynamic difficulties as well as arrhythmias.

Prompt recognition and early treatment of serious arrhythmias have significantly reduced the in-hospital mortality of patients with acute myocardial infarction[1,2] and improved the postoperative management of patients. The surface electrocardiograms commonly used for rhythm monitoring have the disadvantages of signal distortion by patient movement and base-line drift, which make their use difficult for automated monitoring of arrhythmias. Furthermore, differentiation of complex arrhythmias with the use of surface electrograms may be difficult because of uncertainty in identification of the P wave. Direct recording of intraatrial and intraventricular electrograms, which provide large atrial (P wave) and ventricular (QRS) signals, respectively, facilitates the diagnosis of complex arrhythmias.[3–5]

In severely ill patients with heart disease and in patients after major surgery, arrhythmias commonly accompany circulatory problems. Hemodynamic monitoring in such patients with the use of flow-directed balloon catheters is now widely practiced.[6,7] This study reports the development of and initial clinical experience with a balloon flotation catheter used to monitor both cardiac arrhythmias and hemodynamic status.[8] This catheter can also be used for immediate temporary cardiac pacing in case of emergency.

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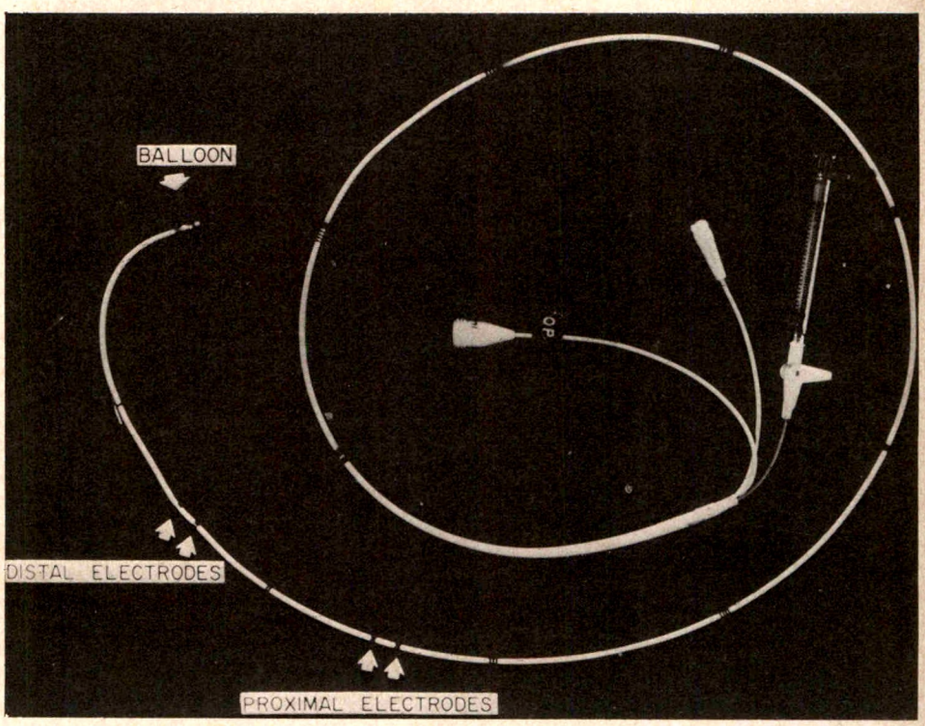

FIGURE 1. Balloon flotation electrode catheter for cardiac monitoring and emergency pacing. The distance from the tip is marked in 10 cm intervals. The position of the proximal (25 and 26 cm) and distal (17 and 18 cm) electrode pairs is indicated by **arrows.** The proximal end of the catheter consists of the lumen for inflation of the balloon, distal lumen and the special adapter for the electrode cables.

Method

Catheter Construction

The basic device (Fig. 1) is essentially similar to the standard flow-directed (Swan-Ganz) catheter[6] but, in addition, incorporates two pairs of electrodes. It is size 7F and extruded from polyvinylchloride with three parallel lumens. One lumen serves to inflate the flow guidance balloon with 1.5 to 2 ml of air. The bursting volume of the balloon is 3 ml. The second lumen opens at the tip and is used for recording of intravascular pressure and withdrawal of blood samples from the central circulation. The third lumen carries the leads from the electrodes, which are properly insulated to prevent current leakage and connected to an adapter proximally. For the average patient the electrodes are located on the shaft of the catheter, 17 and 18 cm and 28 and 29 cm from the tip for the ventricular and atrial electrodes, respectively. When the catheter tip is in the pulmonary artery or its main branches, the proximal (with reference to the catheter tip) electrodes lie in the upper part of the right atrium and the distal electrodes in the right ventricle. The electrical signals are amplified and displayed on an oscilloscope and examples recorded on the Brush recorder.

The catheter shaft is stiffened up to the ventricular electrodes so that an acute angle forms at the site of the distal electrodes between the stiffer proximal and more flexible distal portion. This arrangement carries the electrodes toward the right ventricular endocardium and permits consistent right ventricular endocardial pacing (Fig. 2).

Catheter Insertion

The catheter is inserted at the bedside, usually into a median basilic or deep brachial vein by a cutdown procedure. When the catheter is inserted without fluoroscopic control, intracardiac pressure at the catheter tip and the bipolar electrogram from the proximal pair of electrodes are monitored. The balloon is inflated when the catheter has been advanced 40 cm from the right arm or 50 cm from the left arm. We prefer insertion from the left arm, because passage of the catheter from the right arm is occasionally difficult because of the usual acute angle at the junction of the superior vena cava and the right subclavian vein. When the tip reaches the pulmonary artery, the proximal electrodes record characteristic intraatrial signals and the distal electrodes ventricular signals.

The ideal catheter position is such that the proximal electrodes record a high right atrial electrogram, that is, a large atrial complex (P wave) and a proportionately small ventricular complex (QRS). In this position a characteristic intraventricular electrogram, that is, large QRS complex and very small P wave, is recorded from the distal electrodes and pulmonary arterial pressure is recorded from the tip with the balloon deflated (Fig. 3). When portable fluoroscopic equipment is available in the cardiac care unit, such proper placement of the catheter can be facilitated.

Initial Clinical Trials

The new catheter has been evaluated in 43 patients with a wide variety of cardiac diagnoses, with and without cardiac arrhythmias. Preliminary observations on its value and examples of its application follow.

Ease of insertion: When the catheter was passed at the bedside without fluoroscopy, the passage time to the pulmonary artery was similar to that of the standard (Swan-Ganz) flotation catheters; serious ventricular arrhythmias during passage were uncommon. However, 2 to 11 premature ventricular contractions were observed during the passage of the catheter in 10 of 43 patients.

Stability of intracardiac electrograms: When the catheter was properly positioned, that is, with the

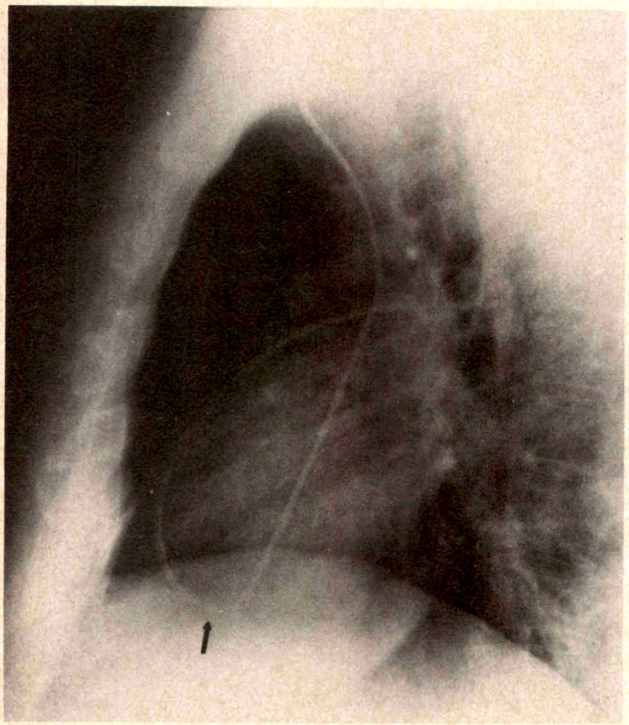

FIGURE 2. Lateral chest X-ray film of a patient with the balloon flotation electrode catheter in position. When the catheter tip is in the pulmonary artery, an acute angle forms in the right ventricular cavity **(arrow).** The distal electrodes are situated at the peak of the angle and thus lie closer to the ventricular endocardium.

proximal electrodes in the high right atrium and distal electrodes in the right ventricle, signals recorded with appropriate filters (atrial, 50 to 300 hertz; ventricular, 15 to 300 hertz) were very stable. There was virtually no base-line drift and respiratory variation was slight. During movement of the patient, when the surface electrogram was distorted by artifacts, both intraatrial and intraventricular electrograms remained free of artifacts (Fig. 4).

Diagnosis of arrhythmias: Simultaneous recording of intraatrial and intraventricular signals facilitates the diagnosis of arrhythmias (Fig. 5). Differentiation between supraventricular tachycardia with aberrant conduction and atrioventricular (A-V) dissociation was not possible from analysis of the surface electrograms. The presence of independent atrial and ventricular signals in the intracavitary electrograms helped in the diagnosis of A-V dissociation.

Emergency pacing: In addition to monitoring intracardiac pressures and cardiac rhythm, this catheter allowed prompt initiation of atrial, ventricular or A-V sequential pacing.

Atrial pacing: With the catheter in the appropriate position, atrial pacing was achieved in the majority of patients (Fig. 6). In 39 of 43 patients, the atrial pacing threshold was less than 6 milliamperes. Temporary atrial pacing for more than 24 hours was performed in two patients. Phrenic nerve stimulation resulting in diaphragmatic contractions occasionally occurred; readjustment of the electrode position and use of minimal current usually resolved this problem. Atrial pacing was inconsistent in the remaining four patients, all of whom had a markedly dilated right atrium. For consistent atrial pacing, proper positioning of the catheter as outlined earlier is essential. Use of fluoroscopy facilitates proper positioning of the proximal electrodes at the right atrial-superior vena caval junction. In patients with cardiomegaly, when the tip of the catheter was in the distant pulmonary arterial branches, the atrial electrodes tended to move into the right atrial cavity and atrial pacing could not be performed. In such circumstances, the catheter needed to be withdrawn to position the atrial electrodes at the atrial-superior vena caval junction to achieve atrial pacing.

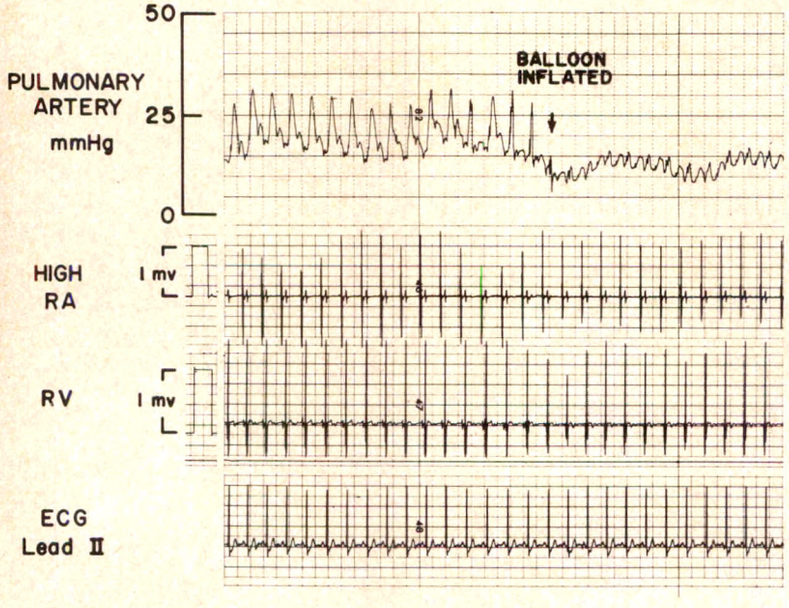

FIGURE 3. Simultaneous recordings of intraatrial and intraventricular electrograms as well as intracardiac pressure with the use of balloon flotation electrode catheter. With the proximal electrodes positioned in the high right atrium, intraatrial electrograms **(upper panel)** demonstrate very large P waves and small QRS complexes. Intraventricular electrograms recorded from the distal electrodes **(middle panel)** show large QRS complexes and very small P waves. Pulmonary arterial pressure (balloon deflated) and pulmonary capillary wedge pressure (balloon inflated) are also recorded **(upper panel).** Lack of base-line drift and noise artifact, despite small catheter movement during inflation of the balloon, is evident in the intracavitary electrograms. ECG = electrocardiogram; RA = right atrium; RV = right ventricle.

· *Ventricular pacing:* Bipolar ventricular pacing with the latest model of the electrode catheters (with greater shaft stiffness than previous models) was reliable and consistent. Thus, satisfactory and uniform ventricular pacing with a threshold of 0.5 to 5 milliamperes could be achieved in 16 of the 17 patients in whom the latest model of the electrode catheter was tested (Fig. 7).

Sequential atrioventricular pacing: In the presence of complete A-V block, A-V pacing could be per-

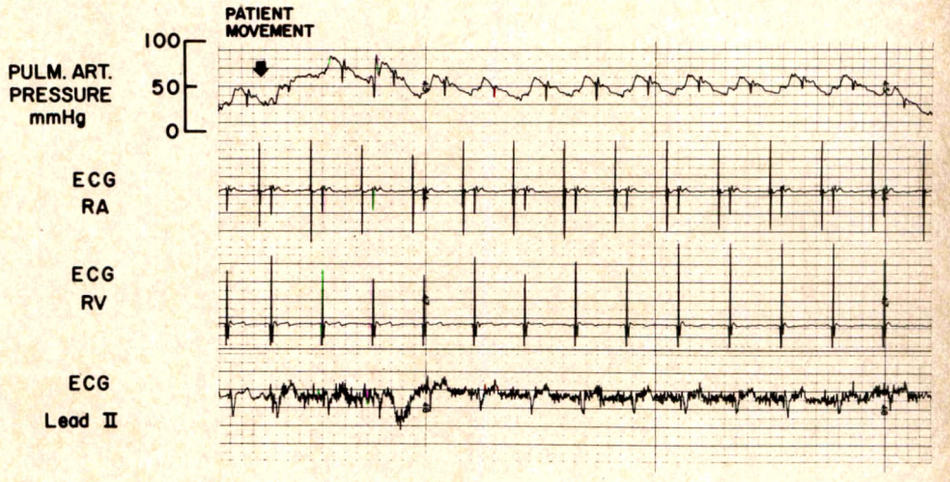

FIGURE 4. Lack of noise artifacts in intracavitary electrograms during movement of the patient. Although recorded surface electrograms are distorted by noise artifact, simultaneously recorded intracavitary electrograms are virtually noise-free. PULM. ART. = pulmonary arterial.

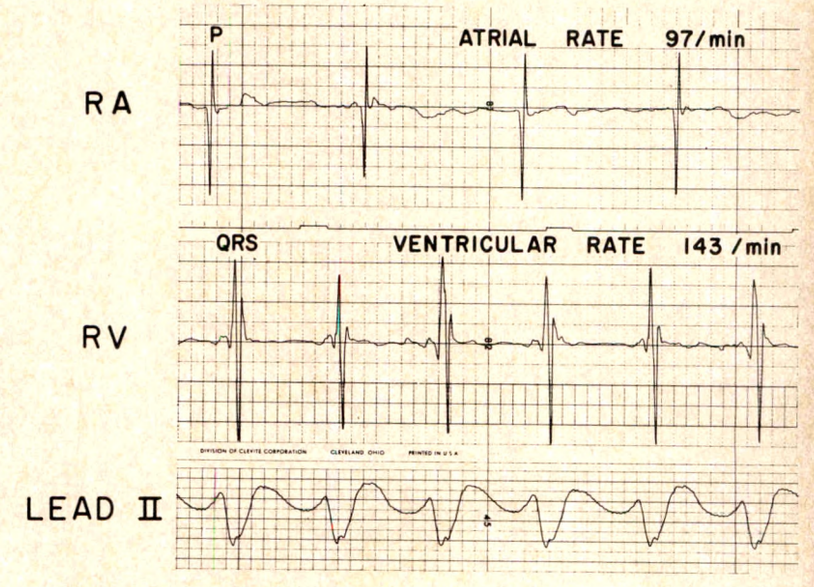

FIGURE 5. Diagnosis of complex arrhythmias from analysis of simultaneously recorded intraatrial and intraventricular signals with the use of balloon flotation electrode catheters. In this instance, differentiation between supraventricular tachycardia with aberrant conduction and ventricular tachycardia with A-V dissociation was not apparent from the surface electrocardiogram. However, the presence of independent atrial and ventricular signals in the intracavitary electrograms establishes the diagnosis of A-V dissociation.

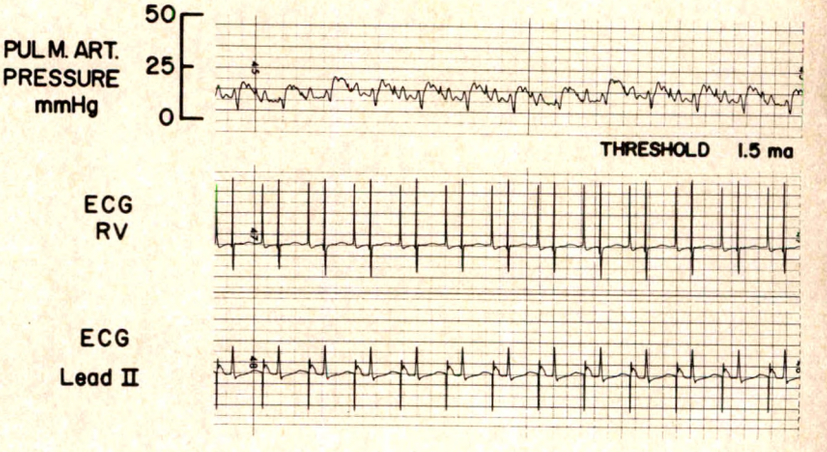

FIGURE 6. Atrial pacing with use of balloon flotation electrode catheters. Consistent atrial pacing could be achieved with a threshold of less than 2 milliamperes.

formed sequentially by using the proximal and distal electrodes for atrial and ventricular stimulation, respectively (Fig. 8). In four patients studied to date, the current needed for sequential pacing did not exceed 6 milliamperes.

Reliable QRS signals for counterpulsation: The distal electrodes can provide very large QRS complexes, virtually free of noise, that can be used for reliable operation of any device requiring a QRS-triggering mechanism. An example is shown in Figure 9. Consistent counterpulsation was achieved when the intraventricular QRS complex was used to trigger the external counterpulsation apparatus, in contrast to frequent misses observed when the surface electrogram was used for triggering.

Hemodynamic monitoring: Like other flow-directed balloon-tipped catheters, this catheter can be used for monitoring intracardiac pressures—pulmonary arterial pressure with the balloon deflated and pulmonary capillary wedge pressure with the balloon inflated. The lumen opening at the tip also permits the withdrawal of blood samples from the central circulation.

Discussion

Intracavitary electrograms from the right atrium and right ventricle have been obtained with ease by

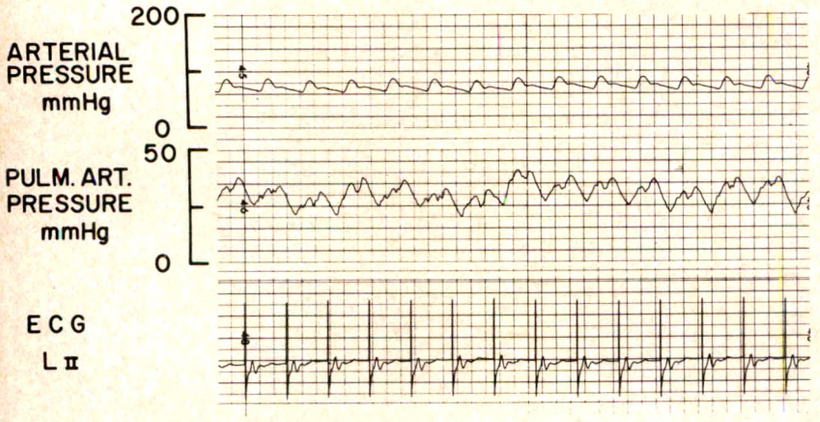

FIGURE 7. Ventricular pacing with use of balloon flotation electrode catheters. Consistent ventricular pacing could be performed with a threshold of 2 milliamperes.

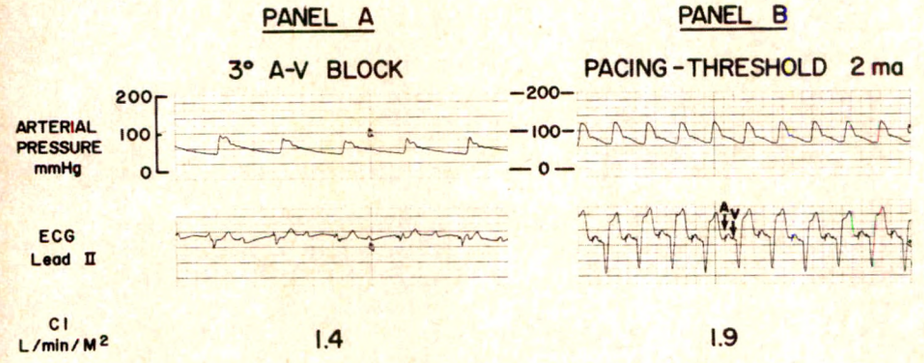

FIGURE 8. Sequential A-V pacing with use of balloon flotation electrode catheters in a patient with acute myocardial infarction complicated by third degree A-V block. Sequential pacing could be achieved with a threshold of 6 milliamperes. Hemodynamics were significantly better during sequential pacing **(Panel B)** than in the presence of complete A-V block **(Panel A).** CI = cardiac index.

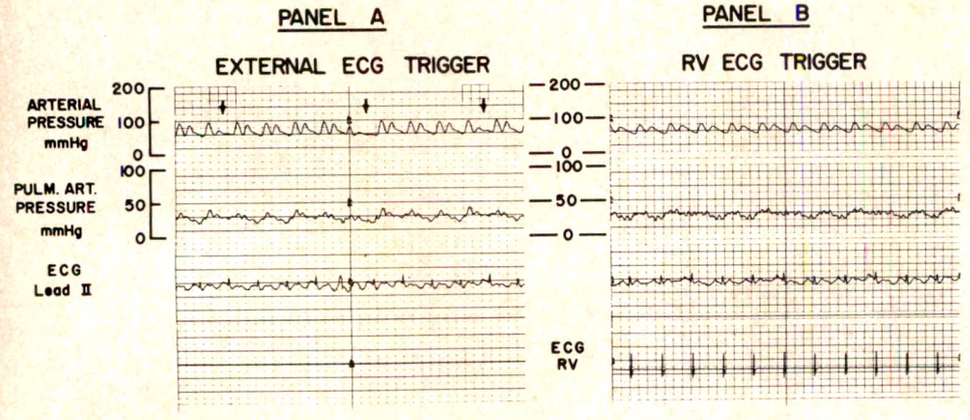

FIGURE 9. Consistent triggering of the external counterpulsation apparatus with the use of large QRS complexes in the right intraventricular (RV) electrogram **(Panel B)** in contrast to frequent misses observed **(arrows)** when the surface electrogram was used for triggering **(Panel A).**

the incorporation of suitable electrodes on the flow-directed (Swan-Ganz) catheter. They offer potential diagnostic advances and provide stabilized signals suitable for computerized monitoring of cardiac rate and rhythm. In our brief clinical experience, no greater difficulty was encountered in insertion than with other Swan-Ganz catheters, and no significant complications were encountered.

Bedside applications: When the catheter was properly positioned, ventricular pacing could be achieved reliably and consistently. In addition, atrial or atrioventricular pacing was usually possible. Several options relative to extended application of bedside catheterization present themselves. First, the technique permits cardiac monitoring without surface leads in cardiac or postoperative patients who require hemodynamic monitoring of ventricular function for which a Swan-Ganz catheter would be inserted. In such patients, reliance on a rate meter to indicate serious arrhythmias would appear feasible.

Because of the increasing number of patients being simultaneously monitored in critical care areas, use of automated on-line computer monitoring of cardiac rhythm is becoming more and more necessary. Bipolar intraatrial and intraventricular electrograms recorded from the proximal and distal pairs of electrodes with appropriate filters provide large atrial (P wave) and ventricular (QRS) signals. In addition, there is no base-line drift and very little respiratory variation, and both atrial and ventricular signals are virtually artifact-free. These characteristics of intracavitary electrograms are particularly suitable for on-line computer monitoring of cardiac rhythm. Admittedly, excessive arm movement may cause displacement of the electrodes and thereby variation in the amplitude of the intracavitary signals. Moderate restraint in the arm movement or subclavian approach of catheter insertion will prevent gross catheter movements.

In patients with complex cardiac arrhythmias, atrial electrograms are not commonly obtained. Use of the present electrode catheter is rapid and safe. The additional availability of simultaneous right ventricular electrograms should considerably strengthen the diagnostic possibilities of such studies. Furthermore, the long-term stability (6 to 24 hours) of such electrodes may allow for therapeutic evaluation of antiarrhythmic agents to be carried out in selected instances, with rational selection of therapy based on more objective data than has been the case. Such data may be recorded and analyzed by portable tape equipment (Avionics).

Both intraatrial and intraventricular electrograms recorded with the use of this catheter are bipolar electrograms; therefore, proper orientation of P and QRS vectors cannot be identified. However, the capability of simultaneously recording clear atrial and ventricular signals may substantially aid in the diagnosis of potentially malignant arrhythmias and conduction disturbances such as ventricular and supraventricular premature beats, tachycardia, atrioventricular dissociation and atrioventricular block.

Prophylactic placement of pacemaker catheters is sometimes indicated in patients with atrioventricular or intraventricular conduction abnormalities. This flotation catheter provides standby pacing ability in addition to hemodynamic monitoring and the benefit of sequential ventricular pacing after spontaneous or induced atrial activation.

Finally, the availability of atrial pacing may permit optimization of the heart rate in a routine manner to achieve the most favorable hemodynamic response. For this purpose, atrial and ventricular electrodes will also be incorporated in certain models of the thermodilution catheter.

Problems: Among the major problems associated with application of balloon-tipped electrode catheters is the need for several catheters with differences in distance between the electrodes and the catheter tip and between electrodes to accommodate heart chambers and great vessels of various sizes. Also, isolated amplifiers of high reliability suitable for these applications are costly at present. Nevertheless, our preliminary experience indicates that important interpretive and practical benefits can be achieved by application of this device.

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Retrograde Catheterization of the Left Atrium in Idiopathic Hypertrophic Subaortic Stenosis

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Retrograde catheterization of the left atrium utilizing the Shirey technique was successfully performed in four patients with idiopathic hypertrophic subaortic stenosis. By traversing the inflow tract of the left ventricle on pullback from the left atrium to the aorta, this method served to separate definitively true hypertrophic subaortic stenosis from cavity obliteration. It was accomplished with relative ease and no complications. In patients with suspected idiopathic hypertrophic subaortic stenosis who are to have retrograde left heart catheterization, this approach to the left atrium is recommended as an alternative to the transseptal technique.

In recent years many noninvasive methods have been developed that greatly assist in the recognition and diagnosis of idiopathic hypertrophic subaortic stenosis. At cardiac catheterization the definitive diagnosis of this condition depends on the hemodynamic demonstration of a dynamic subvalvular obstruction to left ventricular outflow and the angiographic demonstration of narrowing of the left ventricular outflow tract during systole by abnormal anterior motion of the anterior mitral valve leaflet and asymmetric septal hypertrophy.[1,2] Accurate assessment of the subvalvular obstruction is essential for diagnosis and for meaningful evaluation of subsequent therapy. However, intraventricular pressure differences simulating obstruction have been shown to occur with cavity obliteration, producing entrapment and compression of the catheter by cardiac muscle.[3,4]

It is possible to distinguish an intraventricular pressure gradient representing true outflow obstruction from one indicating catheter entrapment by demonstrating that the catheter lies in the inflow tract of the left ventricle at the time that a gradient is recorded. This area, just below the mitral valve, never completely empties in systole and is proximal to the obstructing muscular septum.[2,5] Catheter placement at this site has been accomplished by utilizing the transseptal technique to place a catheter in the left ventricle by way of the left atrium. Simultaneous left ventricular and brachial arterial recordings are obtained to measure the outflow tract gradient as the catheter is drawn back through the left ventricular inflow tract and across the mitral valve. An alternative method of entering the left atrium—retrograde catheterization of the left atrium from the left ventricle, as described by Shirey and Sones[6]—has received little attention. To our knowledge this retrograde method has not been specifically applied for the purpose of validating the intraventricular gradient in patients with suspected idiopathic hypertrophic subaortic stenosis.

We have studied four consecutive patients with hypertrophic subaortic stenosis by retrograde catheterization of the left atrium. Left ventricular outflow tract obstruction was evaluated in each case by recording pressures while withdrawing the catheter from the left atrium to the aorta. Subvalvular left ventricular outflow tract obstruction was documented in each case.

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TABLE I

Clinical Data

Case no.	Age (yr) & Sex	Symptoms	Murmur with Valsalva Maneuver	LVET with AN (% Predicted)	ECG	Chest X-ray Film
1	39M	Chest pain, dyspnea	Increased	...	Left axis deviation	Normal
2	34M	Chest pain	No change	Increased (148%)	WPW type A	LVH
3	32M	None	Increased	Increased (128%)	Q waves in leads II, III, aVF	Normal
4	19M	Chest pain	Increased	Increased (125%)	Axis = −120°	LVH

AN = amyl nitrite inhalation; ECG = electrocardiogram; LVET = left ventricular ejection time; LVH = left ventricular hypertrophy; WPW = Wolff-Parkinson-White syndrome.

TABLE II

Cardiac Catheterization Data

Case no.	State	Pressures (mm Hg)					Left Ventricular Angiogram
		LA Mean	LV Inflow	LV Outflow	Ao	CO	
1	Rest	8	145/6	120/6	120/70	5.9	ASH, SAM
2	Rest	10	220/20	120/20	120/85	4.0	ASH, SAM
3	Amyl nitrite	5	190/15	110/15	110/80	4.6	ASH, SAM
4	Amyl nitrite	20	150/20	70/20	70/45	5.0	ASH, SAM

Ao = aortic pressure (systolic/diastolic); ASH = asymmetric septal hypertrophy; CO = systemic cardiac output (liters/min); LA = left atrial; LV = left ventricular (systolic peak/end-diastolic); SAM = systolic anterior motion of the anterior leaflet of the mitral valve.

Material and Methods

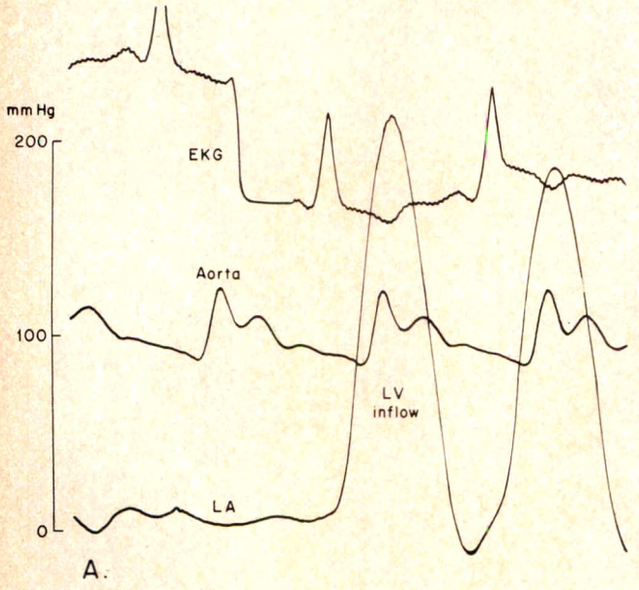
Four consecutive patients with idiopathic hypertrophic subaortic stenosis underwent diagnostic cardiac catheterization. The clinical, hemodynamic and angiographic features of these patients are presented in Tables I and II. All patients had documented physical, hemodynamic and angiographic findings of idiopathic hypertrophic subaortic stenosis.

Phonocardiograms and systolic time interval measurements were made according to the methods of Weissler et al.,[7] using a four channel direct-writing ink jet recorder (Elema Schonander, Mingograf 34). A high impedance microphone (EMT25C) was used for heart sounds and an EMT510C pressure transducer was utilized for recording the carotid arterial tracing. All recordings were obtained simultaneously with electrocardiographic lead II at a paper speed of 100 mm/sec.

Cardiac catheterization was performed with the patient in the postabsorptive state after sedation with intramuscularly administered diazepam or meperidine, or both. Under local anesthesia, the brachial artery and vein were isolated in the right antecubital fossa. With use of the Seldinger technique, a no. 6 Cook multipurpose catheter was introduced into the left brachial artery and advanced into the aorta for pressure monitoring. Left heart catheterization was performed through a brachial arteriotomy with a no. 8 Shirey catheter. Under fluoroscopic observation, the left atrium was entered retrograde with the Shirey catheter with use of the following technique: With continuous pressure monitoring, a large loop was formed in the aorta and prolapsed into the left ventricle; the loop was then rotated to point the tip posteriorly until it crossed the mitral valve and entered the left atrium. A pullback pressure recording was then obtained together with simultaneous aortic pressure tracings (Fig. 1). If no resting gradient was demonstrated, pullback pressure recordings across the mitral valve were obtained after administration of amyl nitrite (Fig. 2). Cardiac output was determined by the Fick method. Left ventricular cineangiography was then performed in the 30° right and 60° left anterior oblique projections.

Results

Clinical features: All four patients had a subvalvular left ventricular outflow gradient documented at the time of cardiac catheterization, and all four had asymmetric septal hypertrophy and abnormal systolic anterior motion of the anterior leaflet of the mitral valve demonstrated by left ventricular angiography (Fig. 3). Three of the patients had chest pain with exertion and one was asymptomatic. The physical examination of all four patients revealed a systolic ejection murmur at the left sternal border. The electrocardiogram was abnormal in each patient. Chest



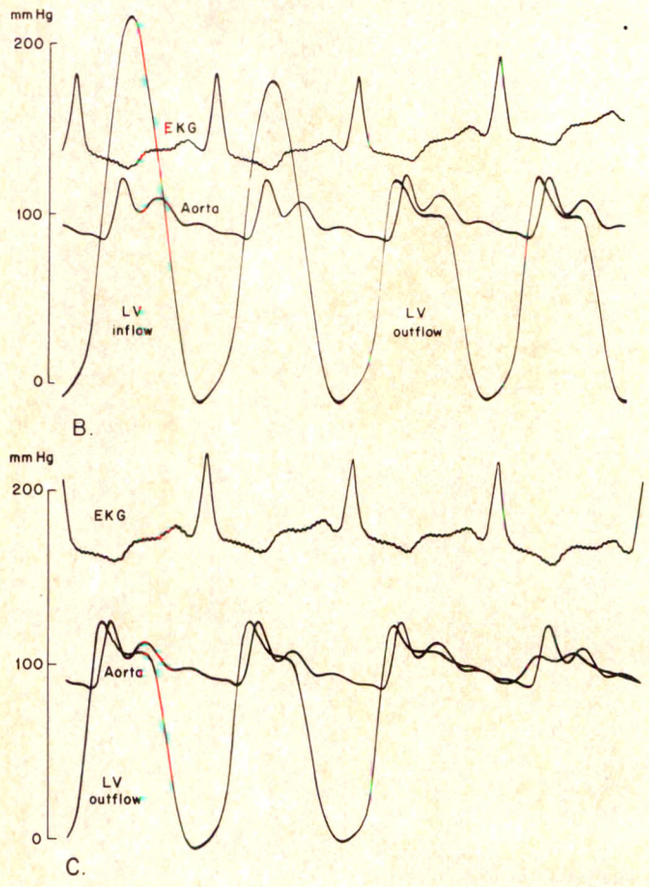


FIGURE 1. Case 2. Continuous retrograde pullback from the left atrium (LA) to the left ventricular (LV) inflow tract **(A)**, the left ventricular inflow tract to the left ventricular outflow tract **(B)** and the left ventricular outflow tract to the aorta **(C)**, with simultaneous recordings of aortic pressure. EKG = electrocardiogram.

roentgenograms revealed left ventricular hypertrophy in two patients and normal findings in two patients.

Intraventricular pressure gradients: Two patients had a resting gradient of 25 and 100 mm Hg, respectively. The third and fourth patients had no gradient at rest but had a gradient of 80 mm Hg after amyl nitrite inhalation (Table II). In each case purposeful catheterization of the left atrium was accomplished without complication. Catheter-induced extrasystoles were frequently encountered but were easily abolished by adjustment of catheter position. There were no episodes of ventricular tachycardia or ventricular fibrillation. The procedure required 15 to 30 minutes from the time the catheter was introduced into the artery until the left atrium was entered. Withdrawal of the Shirey catheter from the left atrium to the left ventricle, with simultaneous recording of aortic pressures, revealed a gradient between the ventricle and the aorta on the first beat recorded from the left ventricle. Pullback to the aorta disclosed the gradient to be subvalvular in all instances.

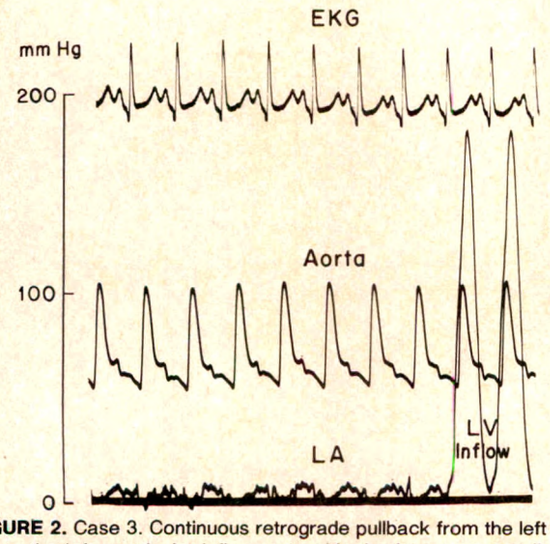


FIGURE 2. Case 3. Continuous retrograde pullback from the left atrium to the left ventricular inflow tract with simultaneous recording of aortic pressure. Tracings recorded during amyl nitrite inhalation.

In one instance (Case 4), the pullback was inadvertently abrupt and the catheter loop was observed to "flip" with a rotary motion from the inflow to the outflow tract of the left ventricle. No gradient was recorded with respect to the aorta on the first intraventricular pressure tracings (Fig. 4, top). On a second withdrawal from the left atrium (Fig. 4, bottom), controlled withdrawal was achieved, and an immediate gradient was documented.

Discussion

Since its description by Ross[8,9] in 1958 the transseptal technique of left heart catheterization has gained wide acceptance. However, it is not a benign

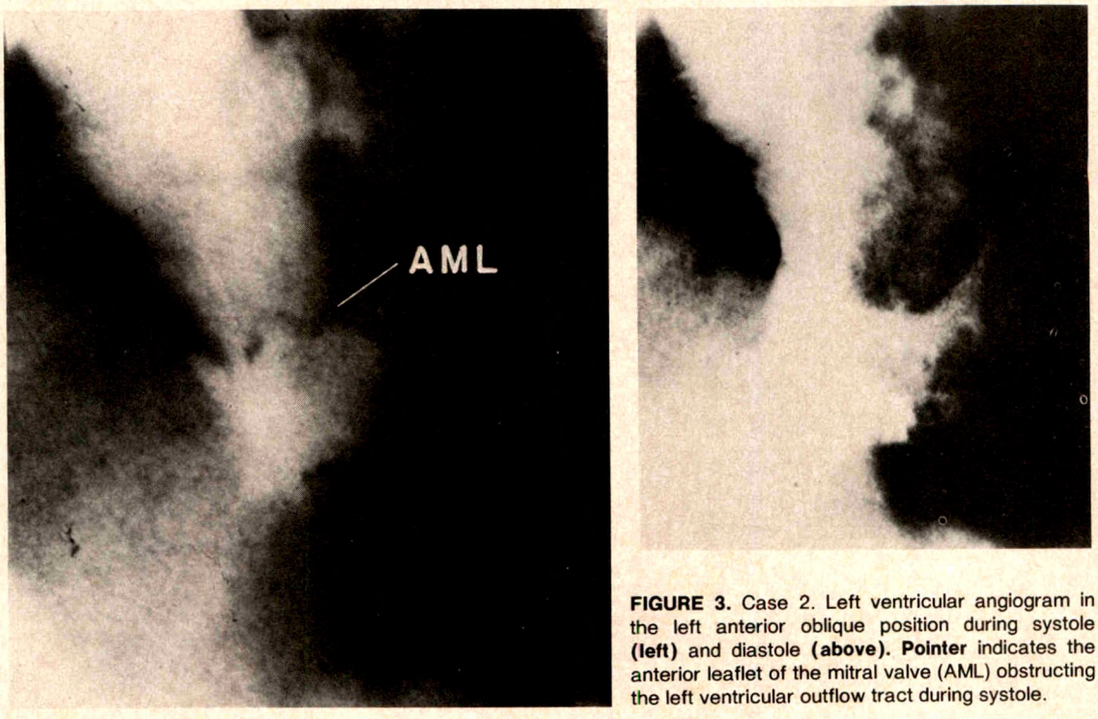


FIGURE 3. Case 2. Left ventricular angiogram in the left anterior oblique position during systole **(left)** and diastole **(above). Pointer** indicates the anterior leaflet of the mitral valve (AML) obstructing the left ventricular outflow tract during systole.

procedure, being associated with a small but significant incidence of complications including inadvertent puncture of the aorta, ventricle and pericardium, pericardial tamponade, retroperitoneal hemorrhage and pulmonary embolism. In 5 to 25 percent of patients the technique is unsuccessful.[10,11] Occasionally physical conditions such as kyphoscoliosis or thrombophlebitis preclude the use of the transseptal approach and an alternative method is required. In recent years, especially since the development of coronary arteriography, retrograde arterial catheterization of the left side of the heart has become almost routine and has decreased the indications for transseptal catheterization of the left heart chambers. In many centers transseptal catheterization of the left heart chambers is now limited to situations in which the pulmonary wedge pressure cannot be obtained (or is not a valid reflection of left atrial pressure), the aortic valve cannot be crossed retrograde, or idiopathic hypertrophic subaortic stenosis is present.

Patients with idiopathic hypertrophic subaortic stenosis must be distinguished from patients with spurious pressure gradients related to cavity obliteration and catheter entrapment. This is of particular importance if surgery is contemplated since patients with cavity obliteration are usually not candidates for surgical intervention. Demonstration of an intraventricular pressure gradient with a high pressure zone on the immediate ventricular side of the mitral valve supports the diagnosis of true muscular obstruction. A catheter in this position cannot be entrapped in left ventricular muscle. One method of guaranteeing proper catheter position is to approach the left ventricle through the left atrium. During a pullback tracing from the left ventricular apex to the left atrium

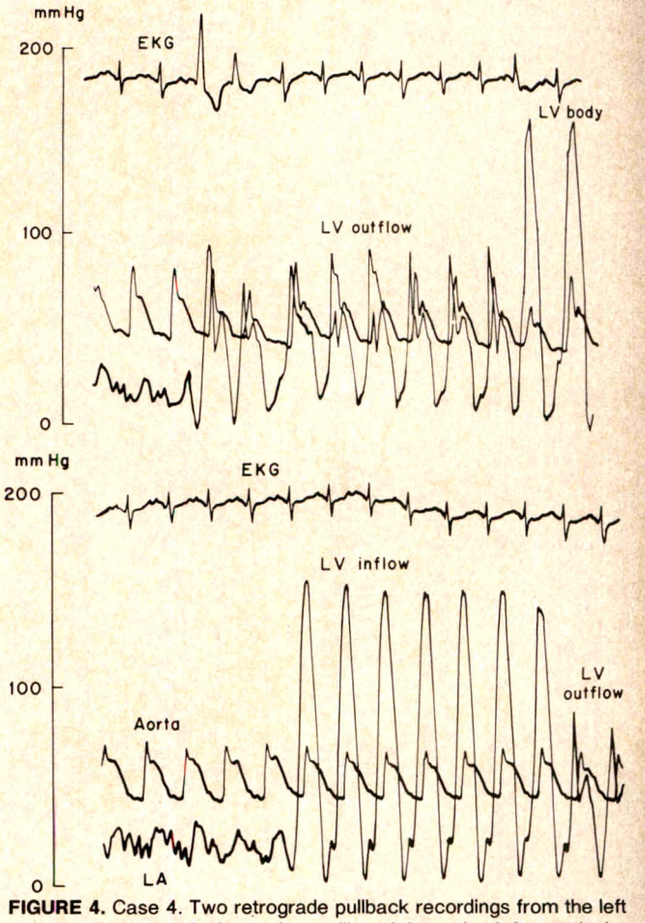


FIGURE 4. Case 4. Two retrograde pullback recordings from the left atrium. In **top panel,** the catheter flipped from the left ventricular (LV) inflow tract to the outflow tract and was then advanced to the body of the left ventricle. In **bottom panel,** a controlled pullback into the inflow tract was observed fluoroscopically.

the catheter traverses the left ventricular inflow tract to distinguish true obstruction from catheter entrapment. Conversely, a catheter introduced in retrograde fashion into the left atrium traverses the same zone when withdrawn from the left atrium to the aorta.

In 1966, Shirey and Sones[6] first described their experience with retrograde left heart catheterization utilizing the Shirey catheter. In their series of 315 patients, the left atrium was successfully entered in 90 percent of cases. The success rate was 85 percent in patients with mitral stenosis and 97 percent in patients with mitral regurgitation. The complications encountered were five episodes of ventricular fibrillation and one episode of ventricular tachycardia, all successfully treated. There were two episodes of hemopericardium related to catheter puncture of the left ventricular myocardium.

The retrograde approach for catheterization of the left atrium in patients with idiopathic hypertrophic subaortic stenosis has been previously mentioned.[2,12] Both Ross et al.[2] and Gault and Simon[12] used the transseptal approach as the method of choice, but in both series there was one patient whose left atrium was entered retrograde. Ross et al. commented that this occurrence was not surprising since the anterior leaflet of the mitral valve was contiguous with the aorta and could be traversed in diastole. Moreover, because significant mitral regurgitation is present in 50 percent of patients with idiopathic hypertrophic subaortic stenosis, one would not expect the retrograde approach to be difficult in these patients. The resting gradient in our four patients with idiopathic hypertrophic subaortic stenosis ranged from none to severe. Three of the four patients had mild mitral regurgitation. Retrograde catheterization of the left atrium was performed with relative ease and with no complications. Catheter-induced extrasystoles often occurred, but there were no episodes of ventricular tachycardia or fibrillation. Even though our laboratory does not use this procedure routinely, the time required to perform it is comparable to that required for transseptal catheterization, and the risk of serious complications is less.

A false negative result can occur, but can be anticipated if the pullback is observed under fluoroscopy. If the catheter loop moves abruptly, with a rotary motion, it can move rapidly from the left ventricular inflow to the outflow tract, entering the infundibulum, and demonstrating no gradient. A slow, controlled withdrawal, without sudden changes in position, is unlikely to yield misleading results.

Thus, if retrograde arterial catheterization of the left side of the heart is proposed for patients with suspected idiopathic hypertrophic subaortic stenosis, we would advocate use of retrograde catheterization of the left atrium. The technique would eliminate the need for transseptal catheterization, with its attendant risk of complications and requirement of a separate entry site.

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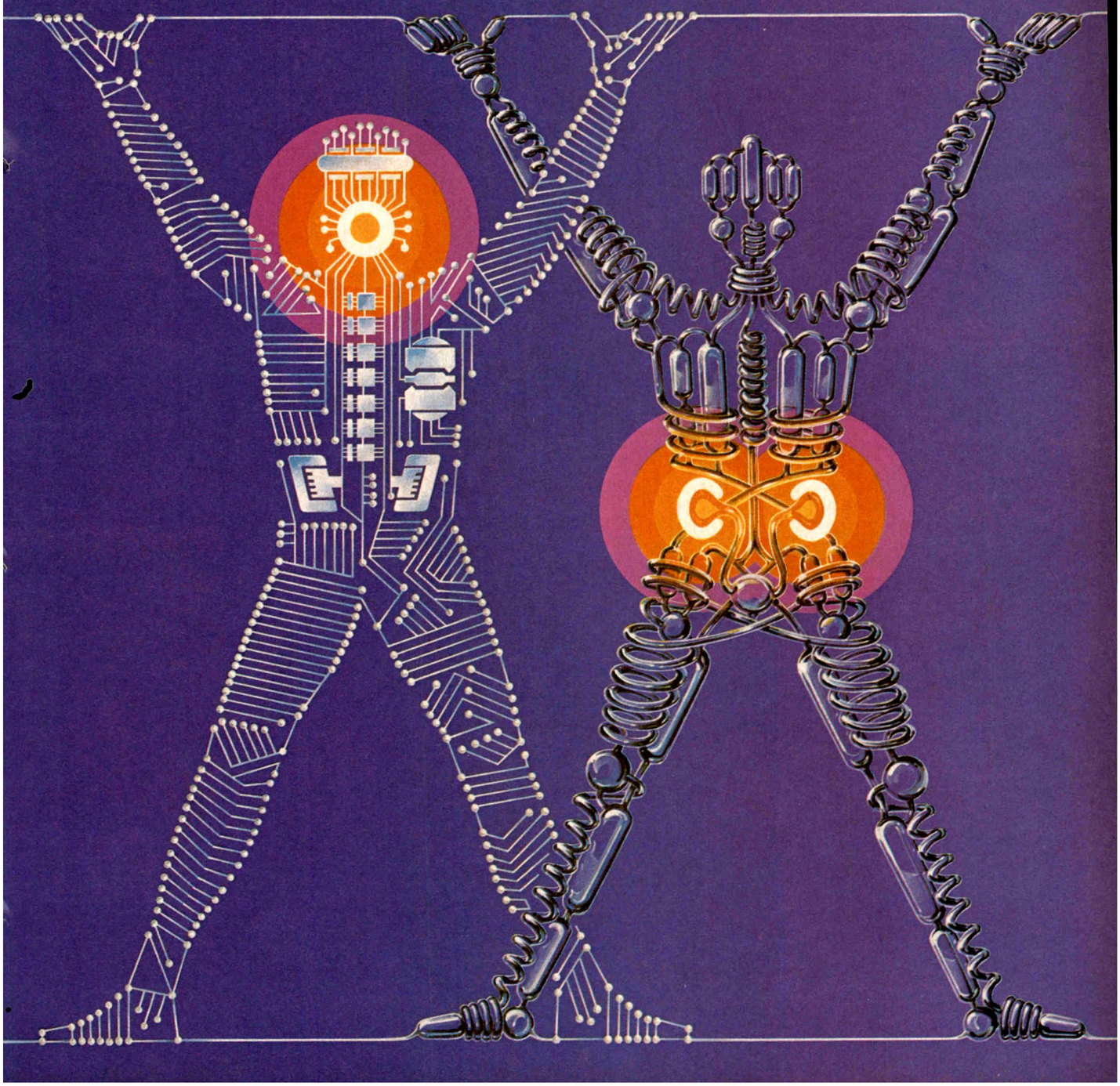

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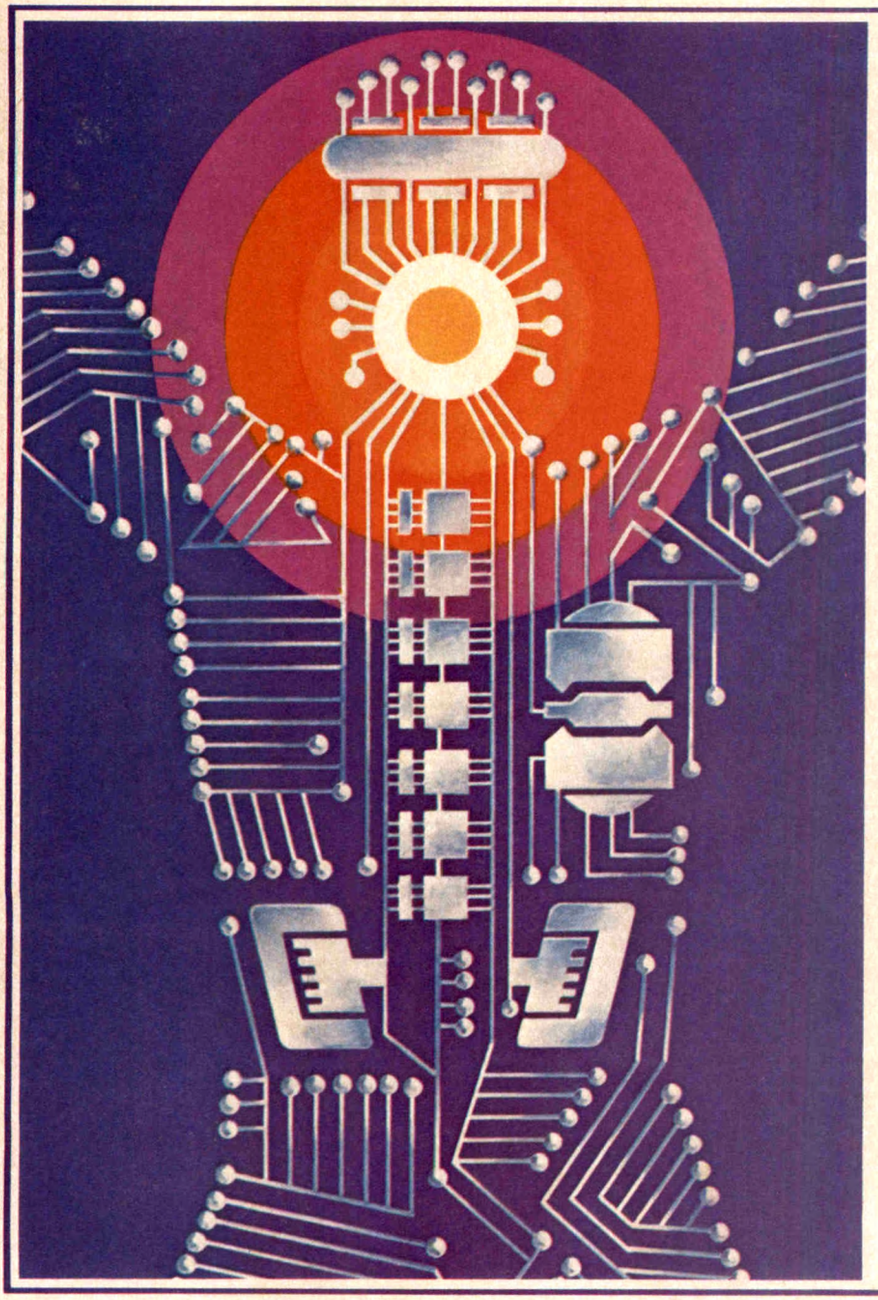

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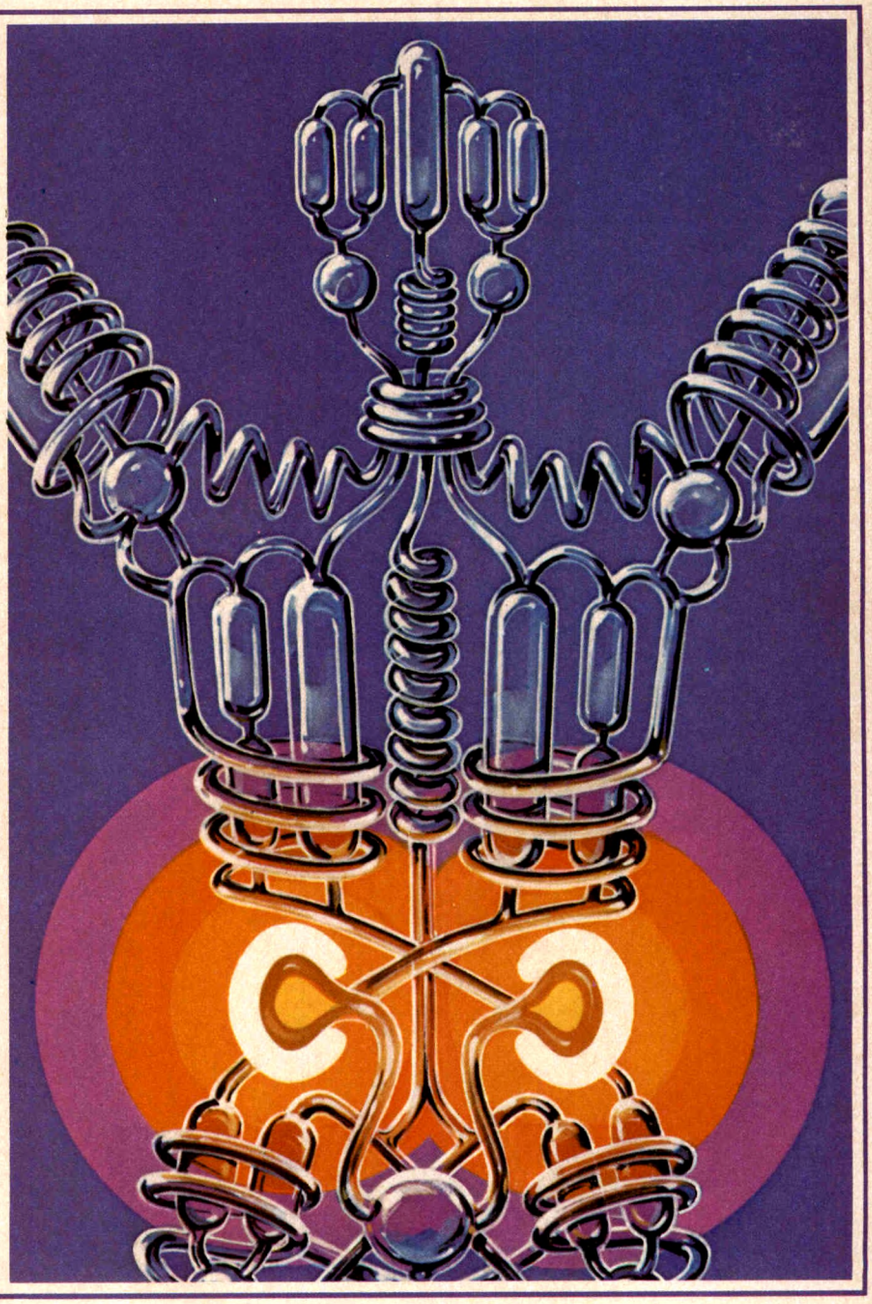

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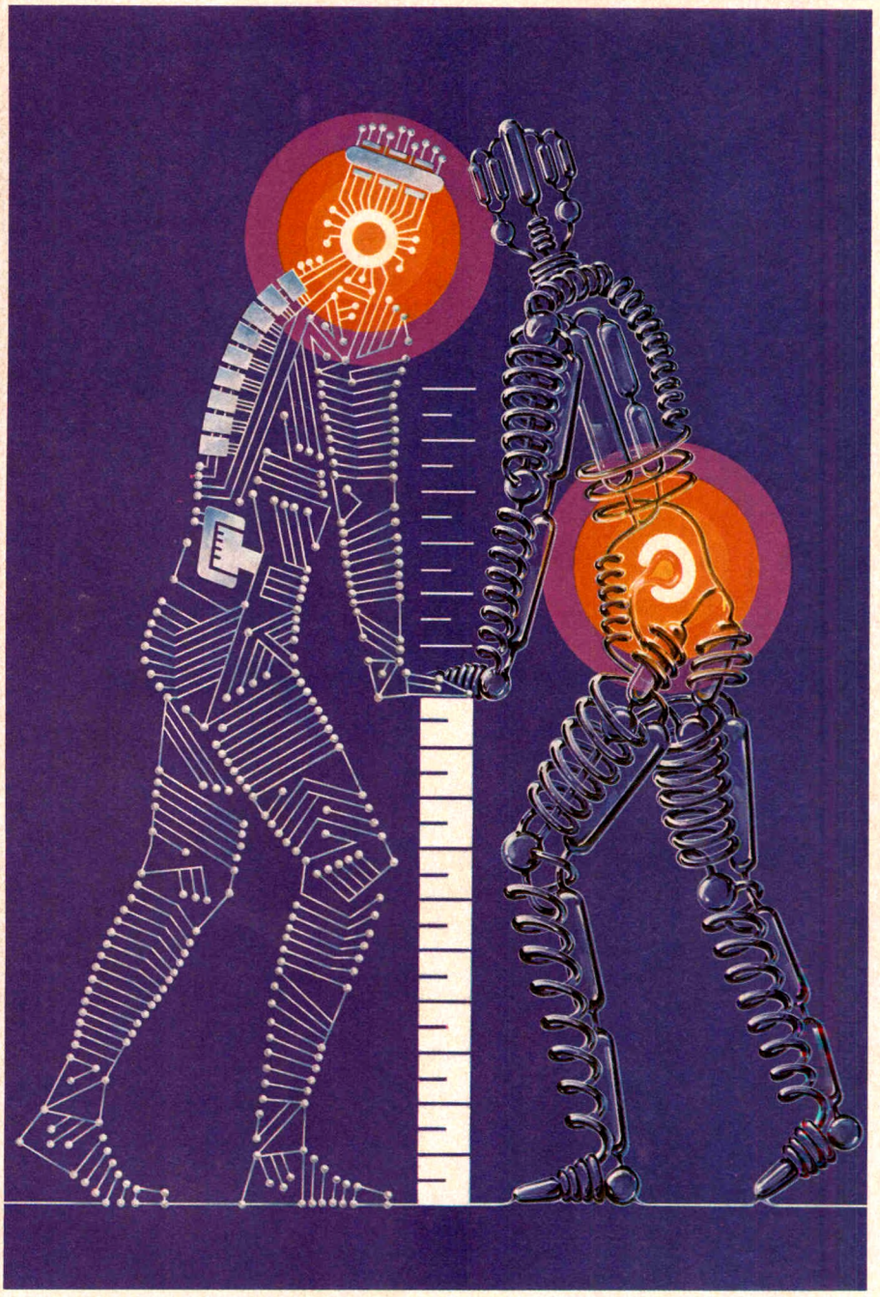

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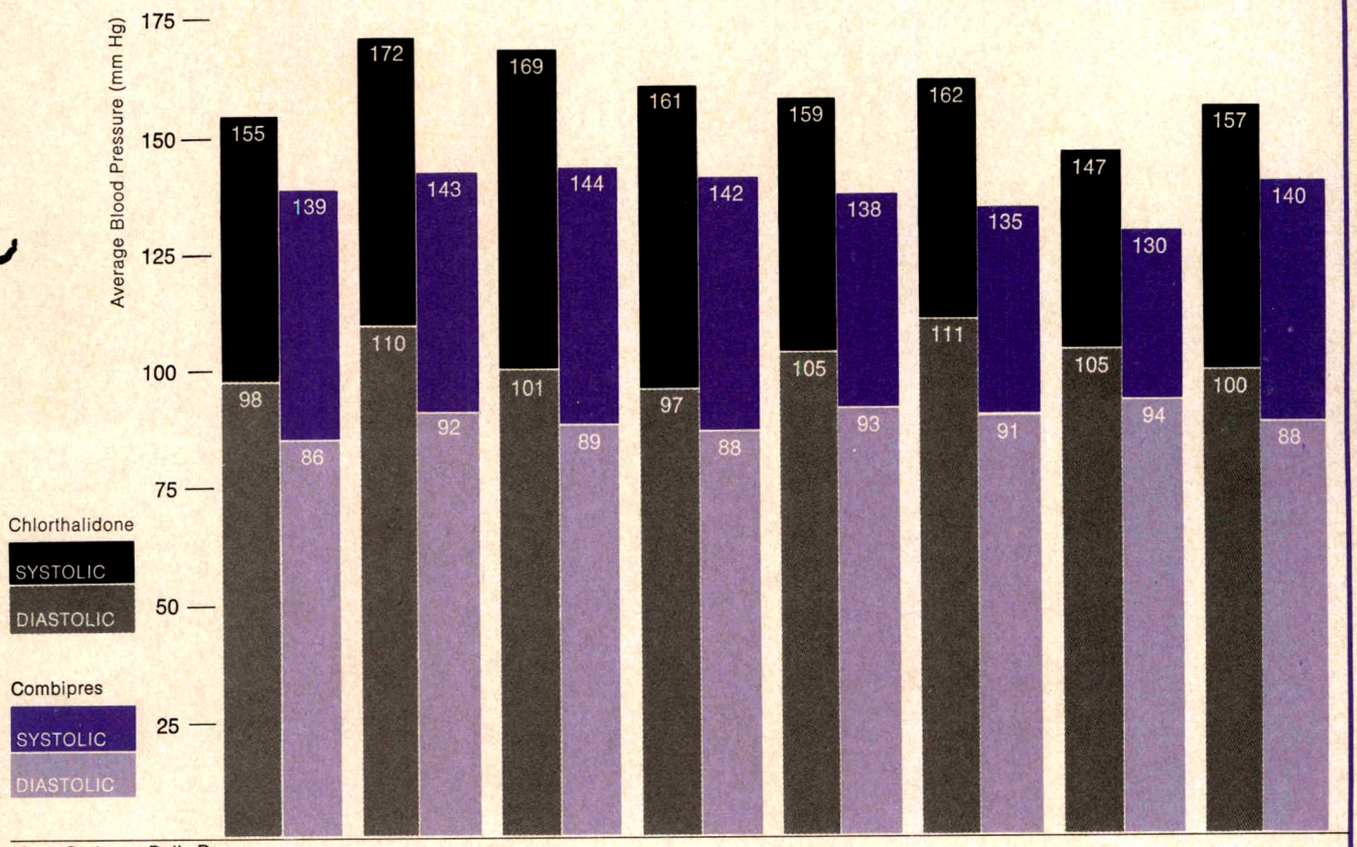

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Study	1	2	3	4	5	6	7	8

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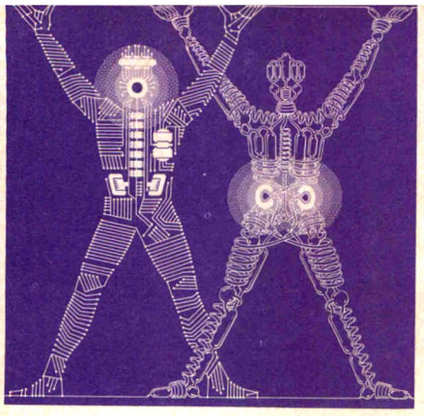

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Guidelines for Titrating Catapres and Chlorthalidone Dosages:

Initial doses: Catapres—one 0.1 mg tablet twice daily. Chlorthalidone—50 mg daily.

Dosage increments: While daily chlorthalidone doses remain at 50 mg, further increments of Catapres of 0.1 mg or 0.2 mg per day can be made at intervals of 2 to 14 days depending on severity of hypertension. The usual daily dose of Catapres ranges between 0.2 and 0.8 mg. Studies indicate that 2.4 mg is the maximum effective daily dose, but doses as high as this have rarely been used.

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Actions: Catapres (clonidine hydrochloride): The mechanism of action appears to be central alpha-adrenergic stimulation as demonstrated in animal studies. This results in inhibition of bulbar sympathetic cardioaccelerator and sympathetic outflow from the brain. Other studies in humans have provided evidence of a reduction in plasma renin activity and the excretion of aldosterone and catecholamines. The exact relationship between these pharmacologic actions of Catapres (clonidine hydrochloride) in humans and its antihypertensive effect has not been fully elucidated at this time.

Chlorthalidone: The diuretic action of chlorthalidone is thought to be due to inhibition of sodium and chloride reabsorption in the proximal tubule.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride, 0.1 mg + chlorthalidone, 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

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For complete details, please see full prescribing information.

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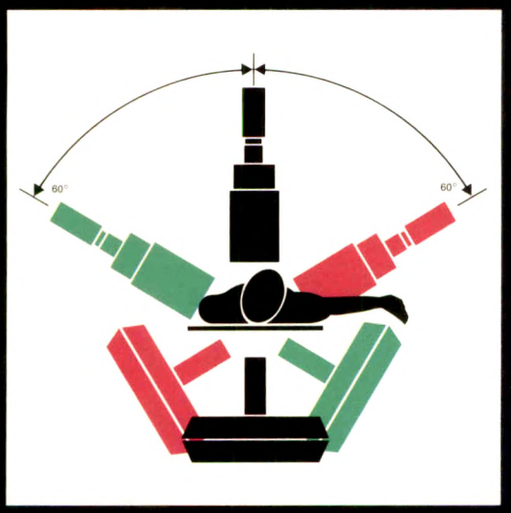

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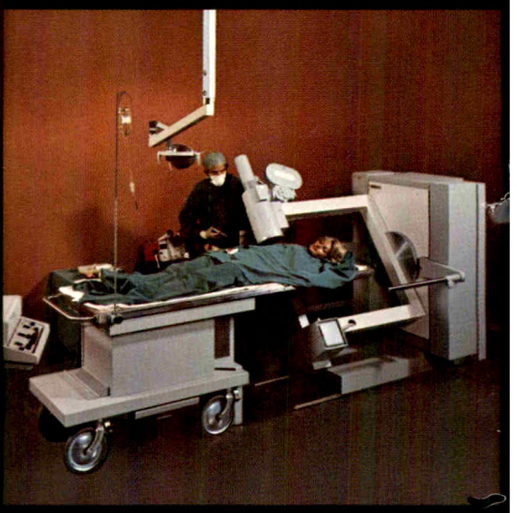

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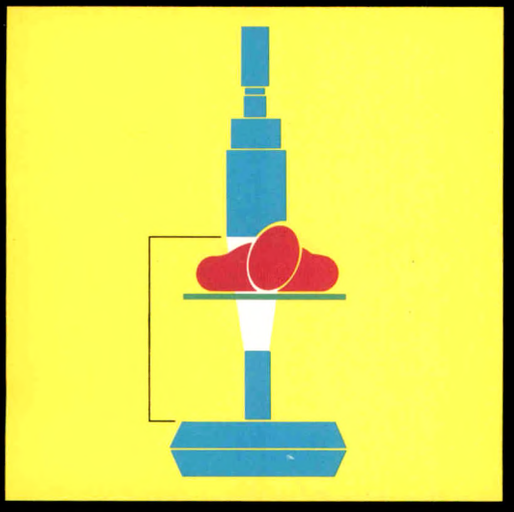

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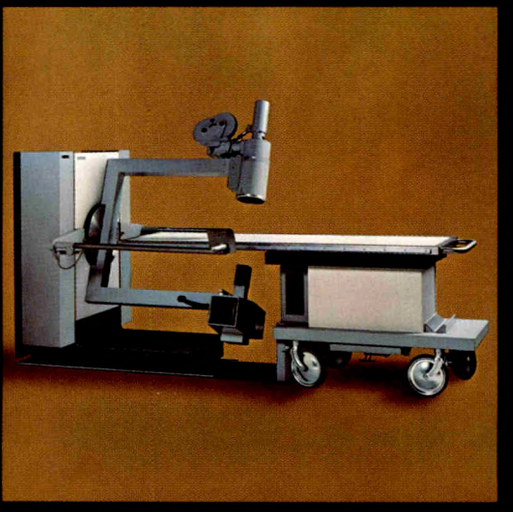

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Circulation

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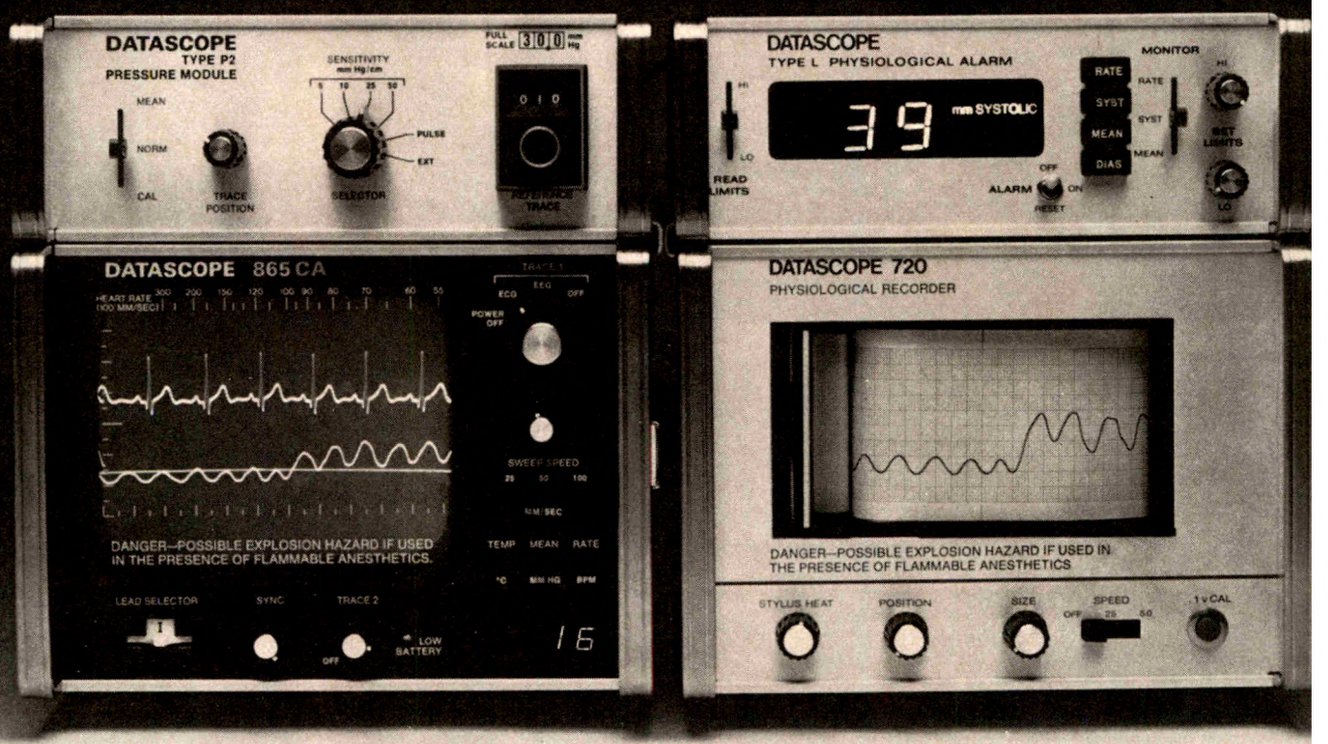

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See brief summary.

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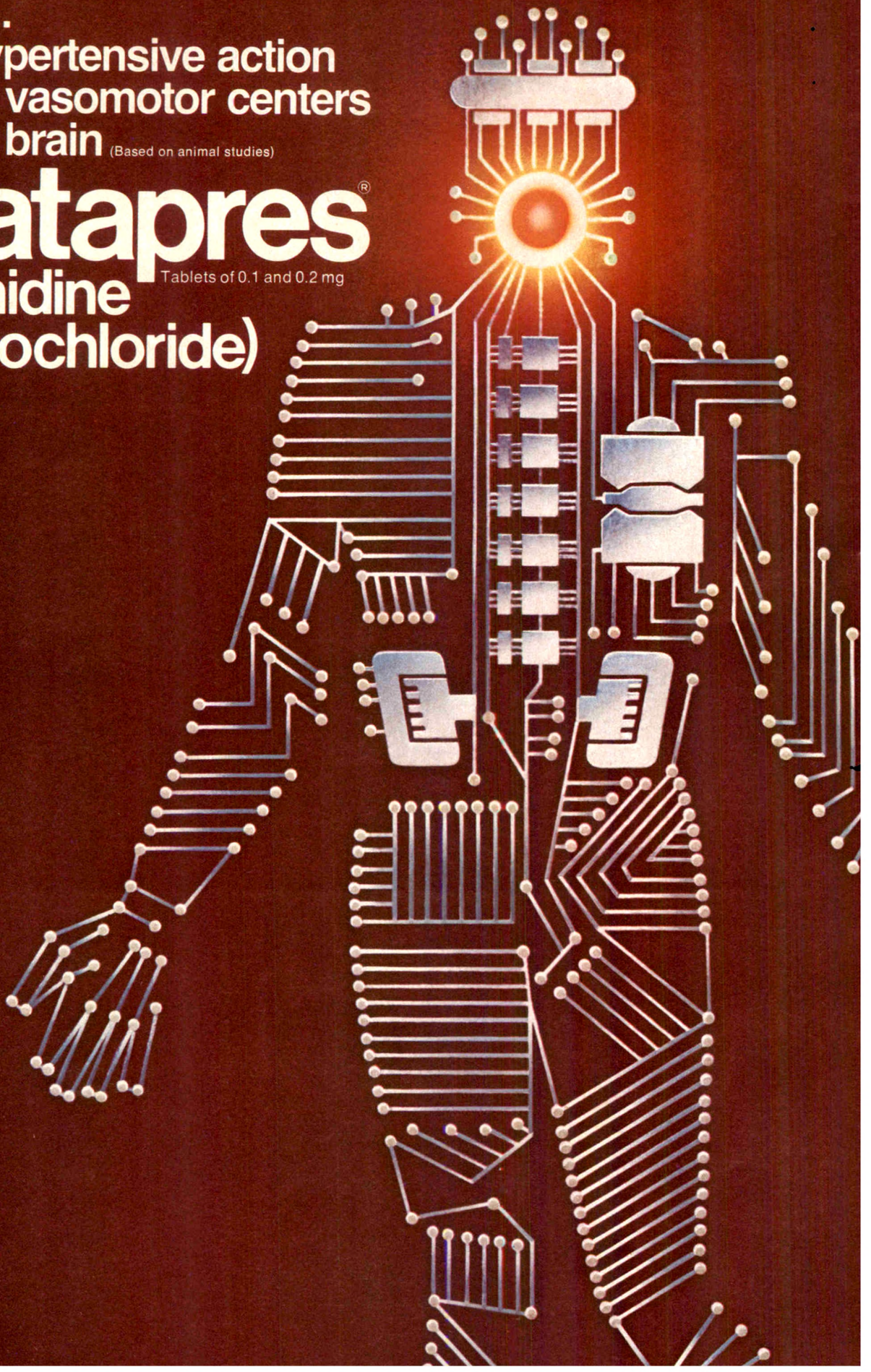

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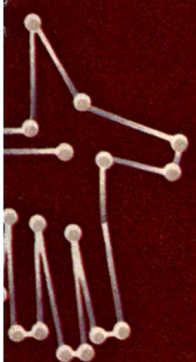

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Mild and infrequent orthostatic hypotension

Normal hemodynamic responses to exercise are unaffected

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Mild to moderate potency

The most common side effects are dry mouth, drowsiness and sedation. These generally tend to diminish with continued therapy. Other potential adverse reactions are listed in the Brief Summary.

Catapres® (clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

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Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established). These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride.

Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

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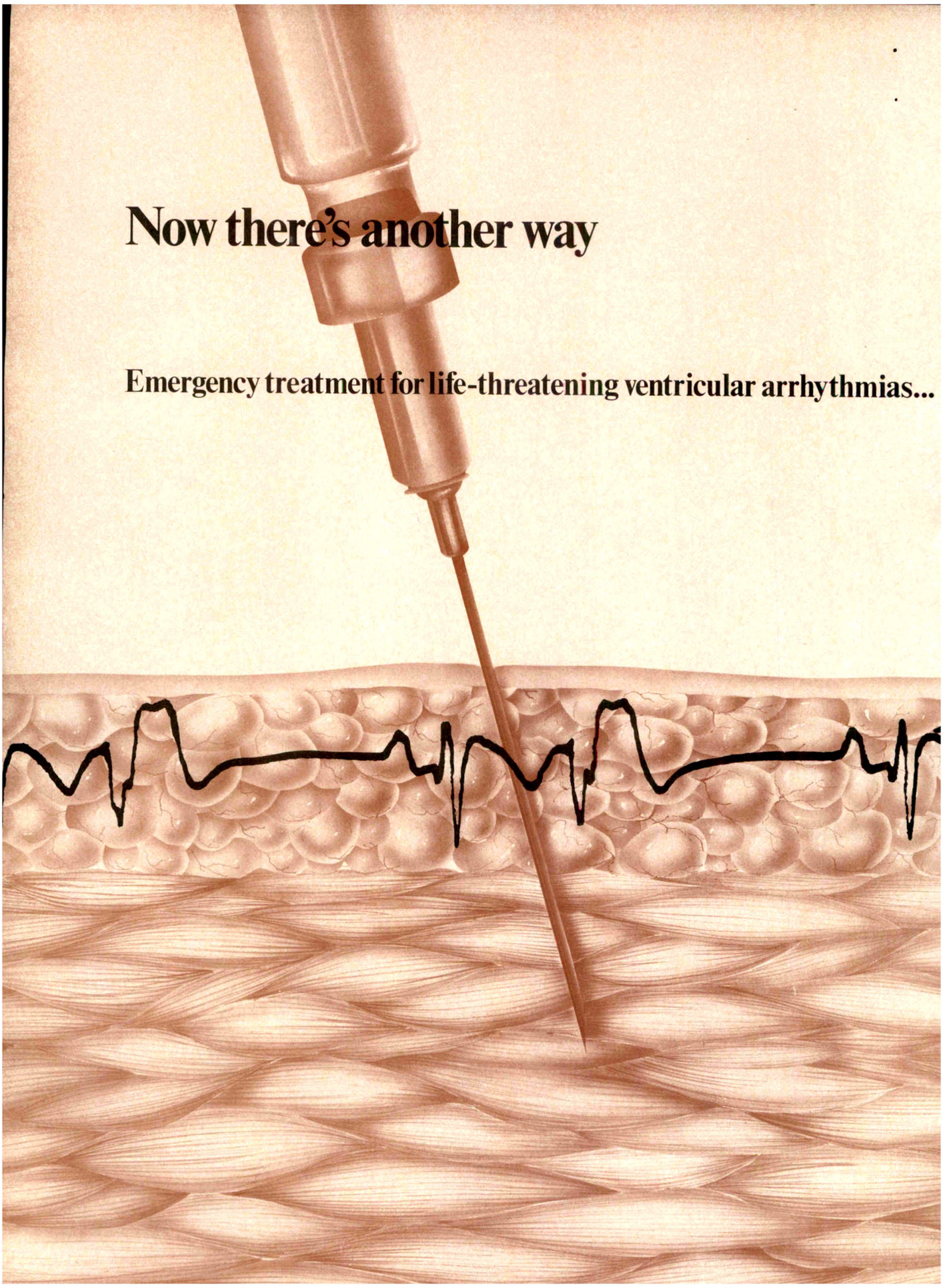
Emergency treatment for life-threatening ventricular arrhythmias...



When an appropriate dose of Xylocaine is administered by the intramuscular (deltoid) route, effective antiarrhythmic blood levels are usually attained within 5-15 minutes and may persist for 60-90 minutes. Xylocaine Intramuscular is specifically indicated in the acute management of life-threatening ventricular arrhythmias when justified:

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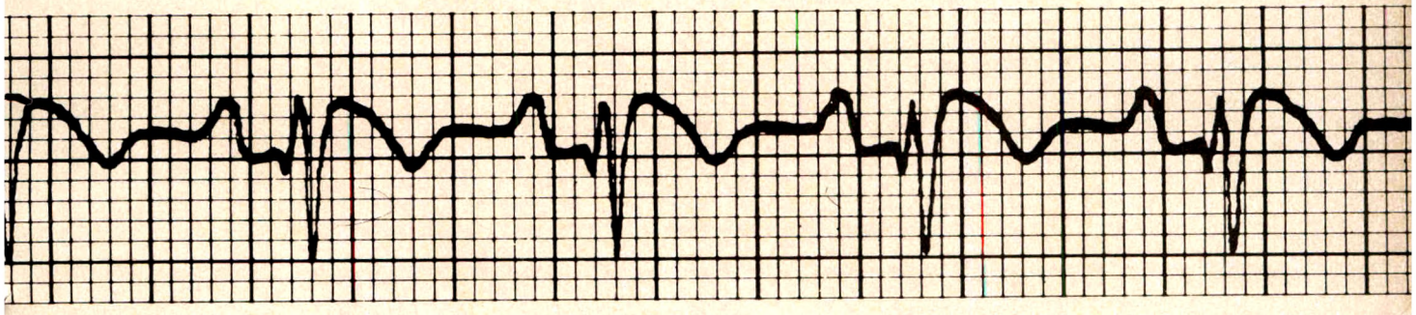

Before prescribing or administering, please consult complete product information, a summary of which follows:

Contraindications: Patients with known hypersensitivity to local anesthetics of the amide type, and patients with Adams-Stokes syndrome or severe degrees of sinoatrial, atrioventricular or intraventricular block.

Warnings: ASPIRATE FREQUENTLY TO AVOID INADVERTENT INTRAVASCULAR ADMINISTRATION.

ECG monitoring is recommended. However, in emergency situations when a physician suspects ventricular arrhythmia and ECG equipment is not available, a single dose may be administered when the physician determines potential benefits outweigh possible risks. If possible, have emergency resuscitative drugs and equipment immediately available to manage potential adverse reactions involving cardiovascular, respiratory, or central nervous systems.

Intramuscular use of Xylocaine® may result in increased creatine phosphokinase levels and compromise the use of this enzyme determination, without isoenzyme separation, in diagnosing acute myocardial infarction.

Pediatric use is not recommended.

Precautions: Observe usual precautions in the presence of impaired renal or hepatic function, hypovolemia and shock, and all forms of heart block.

Adverse Reactions: Although serious adverse reactions to Intramuscular Xylocaine have been rare, the following previously have been reported following lidocaine administration:

1. Central Nervous System—lightheadedness; drowsiness; dizziness; apprehension; euphoria; tinnitus; blurred or double vision; vomiting; sensations of heat, cold, or numbness; twitching; convulsions; unconsciousness; respiratory depression and arrest.
2. Cardiovascular System—hypotension; cardiovascular collapse; bradycardia which may lead to cardiac arrest.

Cross-sensitivity with procainamide or quinidine has not been reported.

Soreness at injection site, occasionally.

Supplied in 5 ml ampules, in cartons of 10. Each ml contains 100 mg of Xylocaine HCl and sodium hydroxide to adjust pH. A 3 ml injection provides the recommended dose.

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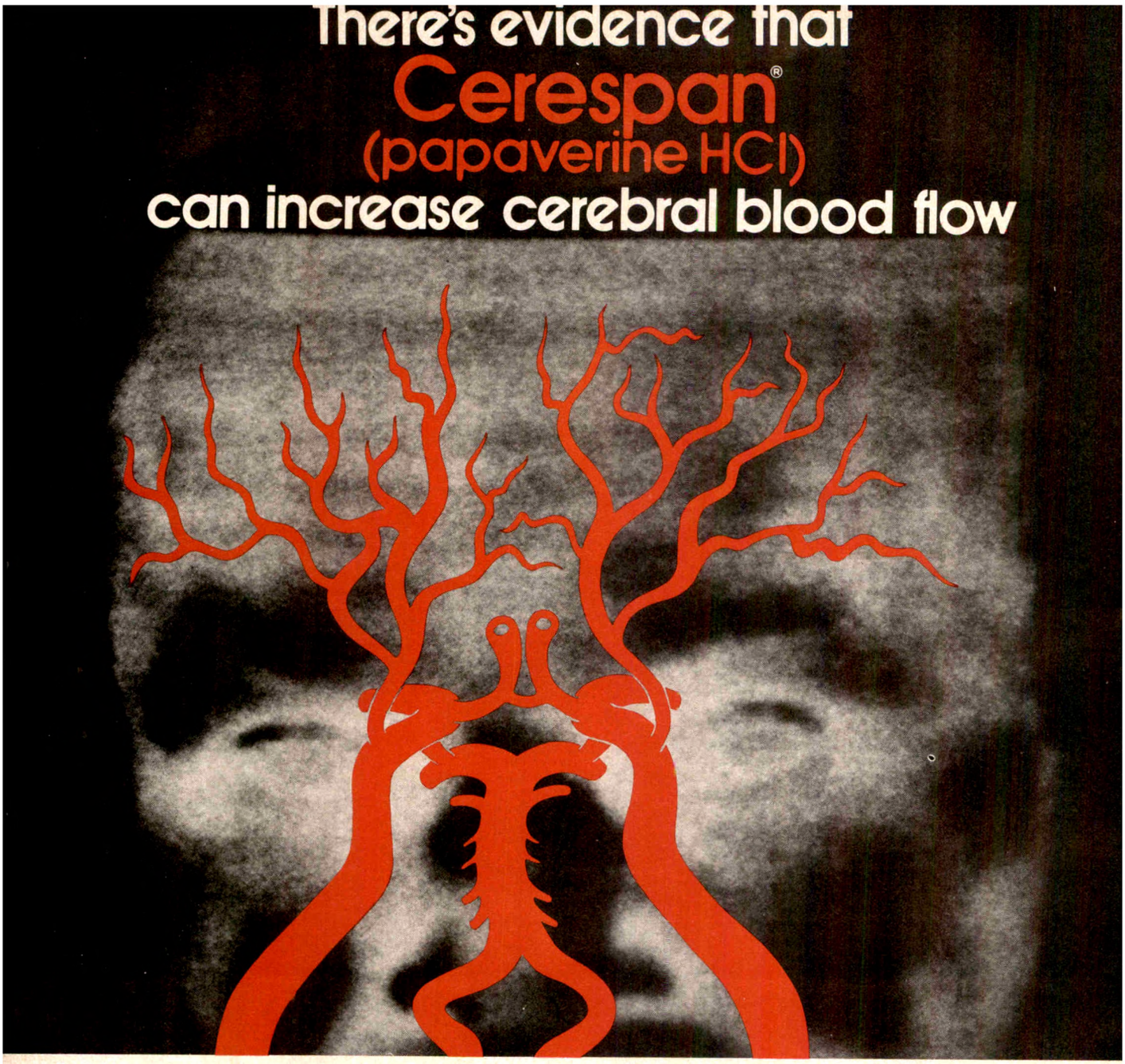
There's evidence that Cerespan® (papaverine HCl) can increase cerebral blood flow



"... improvements in the thermograms were attributed to an increase in cerebral blood flow due to the direct vasodilating effect of Cerespan (papaverine hydrochloride)."*

To help increase blood flow to the brain ... to help lessen the impact of transient ischemic attacks

Simple q. 12 h. dosage encourages adherence to the therapeutic regimen

*Karpman, H. L. and Sheppard, J. J.: Effect of Papaverine Hydrochloride on Cerebral Blood Flow as Measured by Changes in Thermograms in Patients with Cerebrovascular Disease. Data on file, Department of Medical Research, USV Pharmaceutical Corp.

Cerespan® 150 mg. in micro-dialysis cells (papaverine HCl) q. 12 h.

BRIEF SUMMARY: Each Cerespan capsule contains papaverine HCl 150 mg. in micro-dialysis cells.
Indications and Dosage: For relief of cerebral and peripheral ischemia associated with arterial spasm, 1 capsule q. 12 h.
Precautions: Use with caution in glaucoma. Discontinue drug if hepatic hypersensitivity with gastrointestinal symptoms, jaundice, eosinophilia and altered liver function tests occur.
Adverse reactions: Anorexia, nausea, abdominal distress, constipation or diarrhea, skin rash, malaise, drowsiness, vertigo, sweating and headache.
Supplied: Bottles of 100 and 1000; drums of 5000; single-dose blister pack, boxes of 500.

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Right Ventricular Volume in Congenital Heart Disease

ELIZABETH A. FISHER, MD
IRA W. DuBROW, MD
ALOIS R. HASTREITER, MD, FACC

Chicago, Illinois

Methods for angiographic determination of right ventricular volume were compared in right ventricular cast studies and in vivo using a semiautomated Simpson's rule, elliptical and rectangular cross sections and a simple geometric model, a prism with a triangular base. In cast studies excellent correlation coefficients were obtained for all three methods (r = 0.97 to 0.98). In vivo, excellent linear correlation was obtained when the methods were compared (r = 0.98 to 0.99, P <0.001).

Normal mean right ventricular volumes (70 patients) in milliliters per square meter ±1 standard deviation were: end-diastolic volume 64 ± 15, end-systolic volume 25 ± 8 and stroke index 39 ± 11; ejection fraction was 0.61 ± 0.08. Normal mean left ventricular end-diastolic and end-systolic volumes (77 patients) were lower (59 and 19, respectively), and ejection fraction was higher (0.68). Stroke index was the same. Other results showed decreased mean end-diastolic and end-systolic volumes and stroke index, increased ejection fraction (P <0.001, <0.025, <0.025 and <0.005, respectively) in 34 patients with pulmonary stenosis, and increased mean end-diastolic and end-systolic volumes and stroke index (P <0.001, <0.050, <0.001, respectively) in 11 patients with an atrial left to right shunt. In both groups postoperatively, as well as in patients with a ventricular septal defect, tetralogy of Fallot or myocardial disease, mean volumes and ejection fraction were normal.

We conclude that a geometric model can be used to determine right ventricular volume with accuracy. In children, the right ventricle can adapt reversibly to chronic increases in afterload and preload; it is not necessarily overloaded by a ventricular septal defect or tetralogy of Fallot, and it is relatively unaffected by severe myocardial disease.

Simpson's rule has been shown to be an accurate method for angiographic determination of right ventricular volume.[1,2] This method has had limited clinical use and right ventricular volume data are scanty because of the time-consuming and tedious measurements and calculations required when the technique is performed manually. The purpose of this paper is threefold: (1) to describe a semiautomated system for right ventricular volume determination by Simpson's rule; (2) to compare this system with a simple geometric model used as a basis for simplified manual right ventricular volume determination; and (3) to present right ventricular volume data in a large group of infants and children, with both normal and abnormal right ventricles.

Methods

Ventricular Volume Determinations

Right ventricular casts: Radiopaque plastic casts of dog, monkey, baboon and lamb hearts were made, utilizing Batson's no. 17 Anatomical Corrosion Compound (Polysciences, Inc., Rydal, Pa.). Forty-eight casts with right

From the Division of Pediatric Cardiology, University of Illinois Hospital and Abraham Lincoln School of Medicine, Chicago, Ill. This study was supported in part by The University of Illinois Foundation Goodenberger Medical Research Grant 2-44-33-66-3-14. Manuscript accepted November 26, 1974.

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ventricles ranging in volume from 0.36 to 95.48 cc were prepared. The hearts were pressure-fixed[3] and injected with the partially polymerized liquid mixed with barium sulfate paste to make it radiopaque. After the casts hardened the heart tissue was dissected free, the residual tissue was digested with concentrated potassium hydroxide solution, and the respective chamber casts were cut apart. True volumes were determined by water displacement. Radiographic volumes were determined from biplane frontal and lateral radiographs of the casts placed in anatomic position. The films were projected and the cast outlines traced by hand on paper. Plastic grids with 1 by 1 cm lead lines were radiographed at the center of each cast in both projections for purposes of correction for X-ray magnification.

Simpson's rule: Volumes were calculated by Simpson's rule, assuming the cross-sectional areas to be either elliptical or rectangular. Manually, the drawings of the frontal and lateral projections were divided into 10 equally spaced sections by 11 horizontal lines. The volume of each section was $\pi \cdot X/2 \cdot Y/2 \cdot h$ for the elliptical cross section (where X is the frontal diameter and Y is the lateral diameter of the ellipse and h is the height of the section). For the rectangular cross section, the volume of each section was $X \cdot Y \cdot h$ (where X is the frontal length and Y the lateral length of the rectangle and h is the height of the section). The sections were then summed to give the volume of the solid, as

$$\frac{\pi h}{3}\left[\frac{1}{4}(X_0Y_0 + X_{10}Y_{10}) + \right.$$

end segments

$$(X_1Y_1 + X_3Y_3 + \ldots + X_9Y_9) +$$

odd-numbered segments

$$\left.\frac{1}{2}(X_2Y_2 + X_4Y_4 + \ldots + X_8Y_8)\right]$$

even-numbered segments

for the elliptical cross-section and

$$\frac{4h}{3}\left[\frac{1}{4}(X_0Y_0 + X_{10}Y_{10}) + \right.$$

end segments

$$(X_1Y_1 + X_3Y_3 + \ldots + X_9Y_9) +$$

odd-numbered segments

$$\left.\frac{1}{2}(X_2Y_2 + X_4Y_4 + \ldots + X_8Y_8)\right]$$

even-numbered segments

for the rectangular cross section.

By the *semiautomated* method, the drawings were traced with an electronic planimeter (Numonics Corporation, electronic graphics calculator) linked to a programming calculator (Wang 700C series) and plotting output writer (Wang 702 series). Using the X, Y coordinates the calculator was programmed to automatically divide the drawings by horizontal lines spaced at 5 mm intervals and to calculate the volumes by the formulas given above.

Prism method: By inspection of the casts it was considered that a prism with a triangular base was the *simple* geometric solid that most closely corresponded to the shape of the right ventricular casts. The frontal and lateral projections were assumed to be rectangular and to form the sides of a triangle in the horizontal plane.

The model and derivation of the formula for its volume are shown in Figure 1A. Simplified, the formula is $A_f \cdot A_1/2L$, where A_f is the area of the frontal projection, A_1 is the area of the lateral projection and L is the average of the frontal and lateral lengths. Frontal length was measured as the length of a perpendicular drawn between two parallel lines that intersected the top and bottom of the frontal projection. Lateral length was measured from the top of the pulmonary valve to the apex of the lateral projection (Fig. 1B). Areas were determined by planimetry.

For each method, calculated volumes were plotted against true volumes and a linear regression analysis was made.

In vivo volume determinations: Right and left ventricular volumes were determined from biplane cineangiocardiograms performed as a part of routine diagnostic cardiac catheterization studies. All patients were studied in the postabsorptive state. Only patients older than age 6 months were sedated with use of meperidine (Demerol®), promethazine (Phenergan®) and methazine (Sparine®) in intramuscular doses of 0.5 to 1 mg/kg, 0.25 to 0.5 mg/kg and 0.25 to 0.5 mg/kg, respectively. For patients older than age 2 years, additional sedation with droperidol-fentanyl (Innovar®), 0.025 cc/kg up to 1 cc intravenously, was given if required. Biplane cineangiocardiograms were filmed at 64 or 80 frames/sec after the high speed injection of 1 to 2 cc/kg of contrast medium (Conray 400®) into the inferior vena cava or right atrium. Cycles with premature contractions were not used. The earliest cardiac cycle with sufficient contrast to allow accurate tracing of chamber outlines was utilized, and in most cases right and left heart volumes could be determined from the same injection. Correction was made for X-ray magnification by a grid system as described earlier.

Comparison of right and left ventricular volumes: Left ventricular volumes were determined by the standard Dodge biplane method,[4] assuming the left ventricle to be an ellipse of revolution. The volume was calculated as $4\pi/3 \cdot L_1/2 \cdot L_2/2 \cdot L_3/2$, where L_1 = the longer of two lines drawn from the center of the aortic valve to the apex in the frontal and in the lateral projections, L_2 = the short axis of the frontal projection and L_3 = the short axis of the lateral projection. L_1 was measured directly; L_2 and L_3 were calculated by the formulas: $L_2 = 4A_f/\pi L_1$ and $L_3 = 4A_1/\pi L_1$, where A_f and A_1 are the areas of the frontal and lateral projections of the ventricle, respectively. Volumes were corrected by a regression equation determined from left ventricular cast studies: $V' - 0.85V$, where V' = corrected volume and V = calculated volume.

As a test of the methods, angiographic stroke volumes of the right and left ventricles were compared in 91 infants and children with no shunts or valvular insufficiency. Right and left ventricular volumes and ejection fractions were also compared in two groups of patients believed to have normal right or left heart chambers (70 and 77 patients, respectively).

Comparison of methods: Angiographic right ventricular volumes were determined by Simpson's rule (semiautomated method), elliptical and rectangular cross sections and the prism method in 218 infants and children and the results compared after correction with the appropriate regression equations obtained from the cast studies.

Case Material

Normal right ventricular volumes: Right ventricular volume was determined in 70 infants and children believed to have a normal right heart chamber. All patients in this group had a peak systolic pressure of less than 35 mm Hg and an end-diastolic pressure of less than 5 mm Hg in the

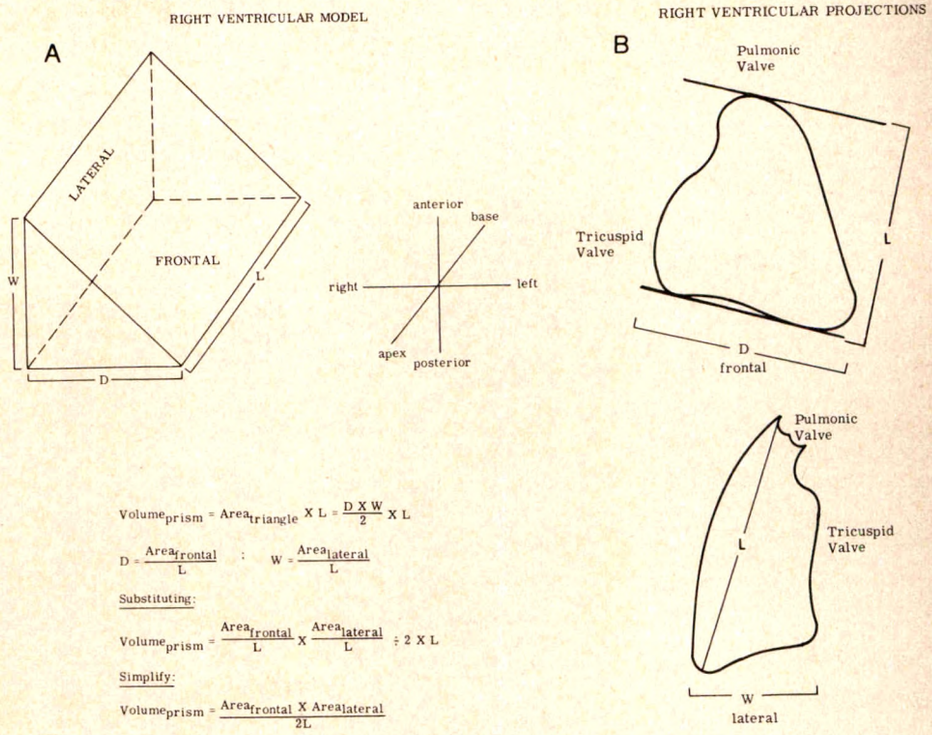

FIGURE 1. Right ventricular model **(A)** and projections **(B).** Corresponding measurements are indicated. D = average width in frontal plane; L = average length; W = average width in lateral plane.

right ventricle. The group contained 31 patients with normal hemodynamic status studied because of arrhythmias, pulmonary disease, mediastinal masses, abnormal electrocardiograms or atypical murmurs. Nine patients had a small patent ductus arteriosus and five had undergone surgical closure of a patent ductus. Four patients had mild pulmonary stenosis (peak systolic gradient less than 15 mm Hg), 10 had mild to moderate aortic stenosis and 2 had undergone surgery for aortic stenosis. Five patients had mild to moderate mitral insufficiency, one mitral stenosis, one mild aortic insufficiency and two systemic hypertension. Their ages ranged from 0.5 to 21.75 years and body surface areas from 0.35 to 1.83 m^2.

Abnormal right ventricular volumes: Five groups of patients with an abnormal right ventricle were studied and the results compared with normal findings.

Group 1 consisted of 44 patients with pulmonary stenosis. Ten of these had undergone surgery at least 1 year previously and had a residual peak systolic gradient from the pulmonary artery to the right ventricle of less than 20 mm Hg and a right ventricular peak systolic pressure less than 40 percent of systemic peak systolic pressure. Only one patient had radiographic cardiac enlargement postoperatively, and he had significant pulmonary insufficiency. The ages of the patients studied postoperatively ranged from 1.75 to 16.5 years and body surface areas from 0.51 to 1.73 m^2. Of the 34 patients studied preoperatively, 20 had a pressure gradient of less than 50 mm Hg; the remainder (14 patients) had a gradient of 50 mm Hg or more. In 8 patients of this group peak right ventricular pressure was less than 40 percent of systemic, in 11 it was 40 to 60 percent, in 7 it was 60 to 100 percent and in 8 it was 100 percent of systemic pressure or greater. The ages of the patients studied preoperatively ranged from 0.75 to 23.0 years and body surface areas from 0.36 to 1.72 m^2.

Group 2 contained 21 patients with a left to right shunt at the atrial level. Eleven of these were studied preoperatively, nine with a secundum atrial septal defect, one with a primum atrial septal defect and one with total anomalous pulmonary venous drainage. Their ages ranged from 0.83 to 16.67 years and body surface areas from 0.31 to 1.60 m^2. Ten patients of this group were studied postoperatively, two who had undergone correction of total anomalous pulmonary venous drainage, one with repair of a secundum atrial septal defect and seven with repair of a primum atrial septal defect. They were studied 0.17 to 5.0 years postoperatively, with seven studied 1 to 2 years postoperatively. Their ages ranged from 0.17 to 16.33 years and body surface areas from 0.34 to 1.70 m^2. None had significant radiographic cardiac enlargement or residual lesions postoperatively.

Group 3 contained 49 patients with a ventricular septal defect. Sixteen had a moderate to large subaortic defect with a pulmonary to systemic blood flow ratio greater than 1.5:1. Fifteen had a small shunt with a pulmonary to systemic flow ratio less than 1.5:1; two in this group had had a previous pulmonary arterial banding. The ages of these 31 patients ranged from 0.04 to 23.42 years and body surface areas from 0.20 to 1.87 m^2. The remaining 18 patients in this group had undergone operation at least 1 year previously. Their ages ranged from 0.45 to 16.33 years and body surface areas from 0.45 to 1.60 m^2. Only one had a large residual defect.

Group 4 contained 22 patients with tetralogy of Fallot, 11 studied preoperatively and 11 studied at least 1 year after operation. In the patients studied postoperatively, ages ranged from 4.67 to 17.42 years and body surface areas from 0.75 to 1.89 m^2. Two had significant pulmonary insufficiency, one manifesting radiographic cardiac enlargement. One postoperative patient had a residual ventricular septal defect with small left to right shunt, and one had significant residual pulmonary stenosis. In the patients studied preoperatively ages ranged from 0.17 to 5.33 years and body surface areas from 0.26 to 0.77 m^2. Although one patient had significant pulmonary insufficiency, his heart size was radiographically normal.

TABLE I

Regression Analysis of Right Ventricular Cast Studies

Method	r value	SEE	Regression Equation
Simpson's ellipse, manual	0.97	5.79	$V' = 0.77V - 2.92$
Simpson's rectangle, manual	0.97	5.79	$V' = 0.60V - 2.99$
Simpson's ellipse, auto	0.97	3.77	$V' = 0.71V - 1.15$
Simpson's rectangle, auto	0.97	3.76	$V' = 0.56V - 1.15$
Prism	0.98	2.94	$V' = 1.16V - 1.04$

auto = semiautomated method; SEE = standard error of the estimate; V = calculated volume; V′ = corrected volume.

Group 5 contained 12 patients believed to have myocardial disease. Ten had endocardial fibroelastosis, three with an associated tiny ventricular septal defect. Two had a primary cardiomyopathy (one due to Pompe's disease and one of unknown origin). All had an abnormal electrocardiogram. Nine manifested left ventricular enlargement, one right ventricular enlargement, one combined ventricular enlargement and one Wolff-Parkinson-White syndrome, type B. Eight had radiographic cardiac enlargement, and six had hepatomegaly at the time of study. Eight had a history of congestive heart failure, but only three had failure at the time of study. Eight patients were receiving digoxin. At cardiac catheterization all standard hemodynamic measurements were normal in seven patients; four had elevated left ventricular end-diastolic pressure, one had elevated right ventricular end-diastolic pressure and one had elevated right and left ventricular end-diastolic pressures. Cardiac output, measured by the Fick method in only four patients, was normal. These patients' ages ranged from 0.08 to 14.98 years and body surface areas from 0.2 to 1.54 m^2.

Results

Right ventricular casts: Regression analysis comparing true and calculated cast volumes (Table I) yielded high correlation coefficients for all methods. Standard errors were low for all methods and lowest (2.94) for the prism method. The Y intercepts for all methods were about 1 cc, making them applicable to calculation of small volumes. For the respective cross-sectional models (ellipse or rectangle), the regression equations for Simpson's rule were quite similar using either the manual or semiautomated method.

In vivo volume determinations—comparison of right and left ventricular volumes: There was a very high correlation between left and right ventricular stroke volumes in patients with no shunts or valvular insufficiency ($r = 0.94$, $P < 0.001$). Normal mean left ventricular end-diastolic and end-systolic volumes were slightly lower, and ejection fraction was slightly higher than corresponding right ventricular values (Table II).

Comparison of methods: The volumes calculated by Simpson's rule, when corrected with the appropriate regression equation from the cast studies, were nearly identical for either elliptical or rectangular cross section ($r = 0.99$, $P < 0.001$). Comparison of these values with those calculated by the prism method also gave excellent correlation for the normal group (Fig. 2A) as well as all abnormal groups (Fig. 2B) ($r = 0.98$, $P < 0.001$ for both). Despite the very high correlation between the prism method and Simpson's rule, in some of the abnormal groups the volumes (compared using the Student t test for paired data) were significantly different (Table III).

In the remainder of this section, all volumes discussed are for Simpson's rule, elliptical cross section. Corresponding values for the prism method are given in Table III.

Normal right ventricular volumes: In the 70 patients believed to have a normal right ventricle, mean end-diastolic volume/m^2 body surface area was 64 ± 15 (1 standard deviation) ml. Only seven of the patients were less than 1 year of age and their mean end-diastolic volume/m^2 was 60 ± 15 ml, not significantly lower than that for the total group or the group over 1 year of age (64 ± 16). There was a high linear correlation of end-diastolic volume with age ($r = 0.87$, $P < 0.001$) and with body surface area ($r = 0.92$, $P < 0.001$). When normal volumes were ex-

TABLE II

Comparison of Right and Left Ventricular Volumes (ml)

Reference	Chamber	Age Group	EDV/m^2	ESV/m^2	SI	EF
Present study	RV	Children	64	25	39	0.61
	LV	Children	59	19	40	0.68
Graham et al.[1]	RV	<1 yr/>1 yr	39/70	13/25	26/45	0.66/0.64
Graham et al.[9]	LV	<2 yr/>2 yr	42/73	13/27	29/46	0.68/0.63
Thilenius	RV	<13 mo/>13 mo	64/78	31/30	33/48	0.52/0.61
and Arcilla[6]	LV	<13 mo/>13 mo	43/66	10/17	34/48	0.79/0.74
Gentzler et al.[2]	RV	Adult	81	39	42	0.51
Kennedy et al.[7]	LV	Adult	70	24	45	0.67

EDV/m^2 = end-diastolic volume per square meter of body surface area; EF = ejection fraction; ESV/m^2 = end-systolic volume per square meter of body surface area; LV = left ventricle; RV = right ventricle; SI = stroke index.

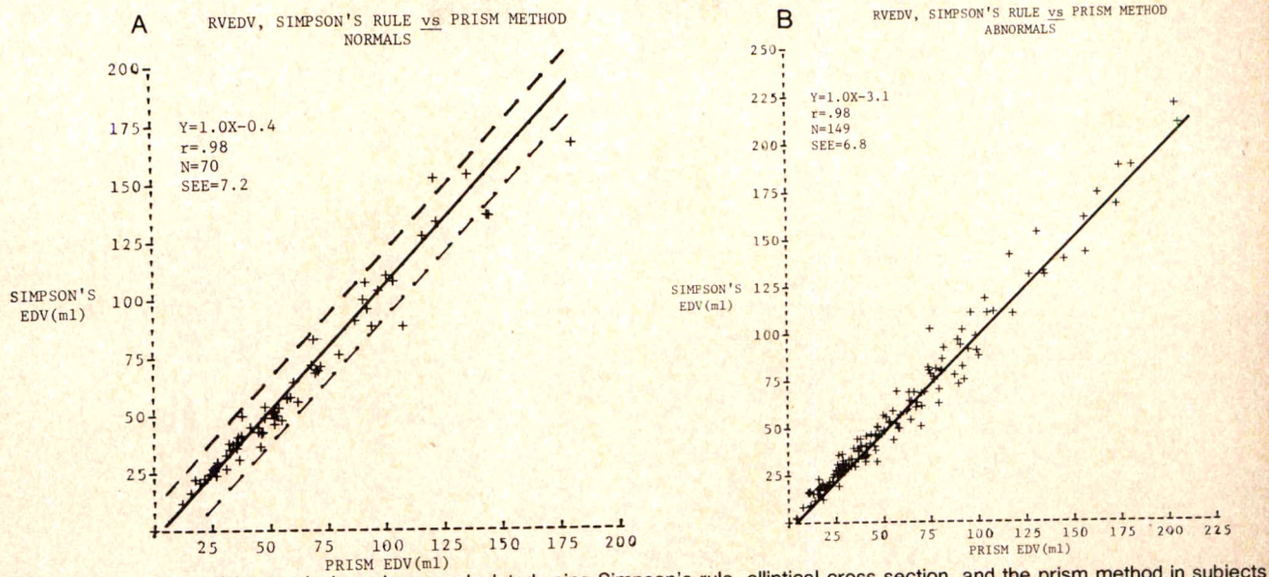

FIGURE 2. Comparison of right ventricular volumes calculated using Simpson's rule, elliptical cross section, and the prism method in subjects with normal **(A)** and abnormal **(B)** conditions. EDV = end-diastolic volume; N = number of cases; RVEDV = right ventricular end-diastolic volume; SEE = standard error of the estimate; X = volume calculated by prism method; Y = volume calculated by Simpson's rule.

pressed per square meter of body surface area, there remained a small but significant correlation with age (r = 0.40, P <0.01). Normal values for end-systolic volume/m^2, stroke index and ejection fraction are given in Table III.

Abnormal right ventricular volumes: The data are summarized in Table III and shown graphically in Figures 3 to 7. *In Group 1* (pulmonary stenosis) values for mean end-diastolic volume/m^2, end-systolic volume/m^2 and stroke index were below normal (P <0.001, <0.025 and <0.025, respectively). Mean ejection fraction was higher than normal (P <0.005). Six patients had an end-diastolic volume/m^2 more than 2 standard deviations below the normal mean value. In these patients right ventricular pressure was 35 percent of systemic pressure in one, 57 percent of systemic pressure in one and from 84 to 113 percent of systemic pressure in four. When the subjects were considered as groups with a right ventricular pressure of less than 40 percent, 40 to 60 percent, 60 to 100 percent and 100 percent or more of systemic pressure, respectively, mean volumes were not statistically different for the groups (end-diastolic volume/m^2 51 ± 11, 52 ± 14, 41 ± 14 and 56 ± 18, respectively). The third group (right ventricular pressure 60 to 100 percent of systemic pressure) contained four of the six patients with an end-diastolic volume more than 2 standard deviations below the normal mean value. When end-diastolic volume in milliliters was plotted against body surface area (Fig. 3) four points fell outside the 90 percent confidence limits for normal subjects. These corresponded to two patients with a right ventricular pressure 60 to 100 percent of systemic pressure, one patient with a right ventricular pressure 40 to 60 percent of systemic pressure and one with a right ventricular pressure less than 40 percent of systemic pressure. Postoperatively, mean volumes and ejection fraction were normal. The one patient with an end-diastolic volume more than 2 standard deviations above the normal mean value had pulmonary insufficiency and radiographic cardiac enlargement.

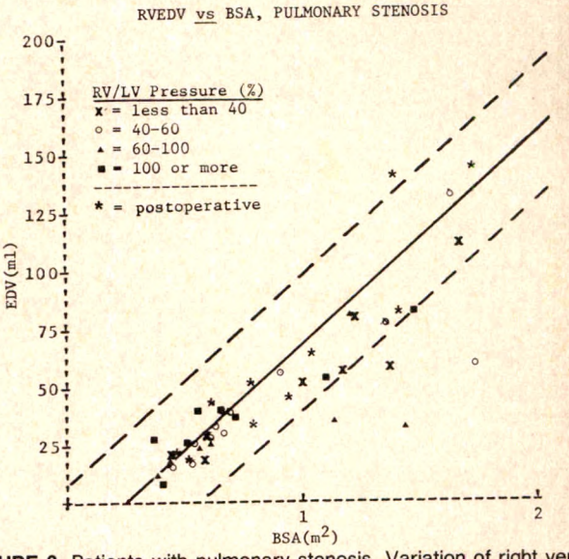

FIGURE 3. Patients with pulmonary stenosis. Variation of right ventricular end-diastolic volume (RVEDV) with body surface area (BSA). Normal mean and 90 percent confidence limits are indicated by the **solid** and **dashed lines,** respectively. LV = left ventricular; RV = right ventricular.

In Group 2 (atrial left to right shunt) mean volumes were considerably above normal (end-diastolic volume/m^2, P <0.001; end-systolic volume/m^2, P <0.050; stroke index, P <0.001), but ejection fraction was normal. Postoperatively, volumes were at normal levels.

TABLE III

Right Ventricular Volumes

			Preoperative								Postoperative								
			EDV/m² (ml)		ESV/m² (ml)		SI (ml)		EF			EDV/m² (ml)		ESV/m² (ml)		SI (ml)		EF	
Group	no.	Method	Mean ± 1 SD	*P*	Mean ± 1 SD	*P*	Mean ± 1 SD	*P*	Mean ± 1 SD	*P*	no.	Mean ± 1 SD	*P*	Mean 1± SD	*P*	Mean 1± SD	*P*	Mean 1± SD	*P*
N	70	S	64 ± 15	...	25 ± 8	...	39 ± 11	...	0.61 ± 0.08	...	...	...	...	...	...	...	...	...	...
		P	64 ± 15	...	25 ± 7	...	39 ± 10	...	0.61 ± 0.07	...	...	...	...	...	...	...	...	...	...
		D	NS	...	NS	...	NS	...	NS	...	...	...	...	...	...	...	...	...	...
PS	34	S	50 ± 15	<0.001	17 ± 7	<0.025	34 ± 11	<0.025	0.67 ± 0.09	<0.005	10	61 ± 20	NS	24 ± 10	NS	37 ± 13	NS	0.61 ± 0.09	NS
		P	53 ± 14	<0.005	18 ± 7	<0.050	34 ± 10	<0.050	0.65 ± 0.09	<0.010		66 ± 20	NS	26 ± 10	NS	40 ± 13	NS	0.61 ± 0.07	NS
		D	<0.050	...	<0.010	...	NS	...	<0.050	...		<0.025	...	NS	...	<0.050	...	NS	...
ASD	11	S	109 ± 28	<0.001	46 ± 12	<0.050	62 ± 24	<0.001	0.56 ± 0.11	NS	10	71 ± 14	NS	25 ± 7	NS	46 ± 11	NS	0.65 ± 0.08	NS
		P	114 ± 27	<0.001	48 ± 13	<0.025	65 ± 20	<0.001	0.57 ± 0.08	NS		75 ± 16	NS	28 ± 7	NS	48 ± 11	<0.050	0.63 ± 0.05	NS
		D	NS	...	NS	...	NS	...	NS	...		NS	...	NS	...	NS	...	NS	...
VSD	31	S	61 ± 19	NS	24 ± 8	NS	37 ± 13	NS	0.60 ± 0.07	NS	18	66 ± 15	NS	28 ± 9	NS	37 ± 9	NS	0.57 ± 0.07	NS
		P	65 ± 18	NS	26 ± 8	NS	39 ± 12	NS	0.60 ± 0.06	NS		67 ± 14	NS	30 ± 12	NS	37 ± 9	NS	0.56 ± 0.10	<0.05
		D	<0.025	...	NS	...	NS	...	NS	...		NS	...	NS	...	NS	...	NS	...
ToF	11	S	61 ± 31	NS	22 ± 13	NS	38 ± 21	NS	0.62 ± 0.11	NS	11	70 ± 17	NS	31 ± 14	NS	40 ± 10	NS	0.57 ± 0.11	NS
		P	65 ± 23	NS	23 ± 10	NS	42 ± 16	NS	0.65 ± 0.10	NS		71 ± 17	NS	31 ± 13	NS	40 ± 10	NS	0.57 ± 0.10	NS
		D	NS	...	NS	...	NS	...	NS	...		NS	...	NS	...	NS	...	NS	...
Myo	12	S	77 ± 40	NS	37 ± 27	NS	39 ± 17	NS	0.56 ± 0.13	NS	...	...	...	...	...	...	...	...	...
		P	79 ± 38	NS	39 ± 27	NS	38 ± 19	NS	0.51 ± 0.15	<0.005	...	...	...	...	...	...	...	...	...
		D	NS	...	NS	...	NS	...	NS	...	...	...	...	...	...	...	...	...	...

ASD = atrial left to right shunt; D = difference between volumes by Simpson's rule and by prism method; Myo = myocardial disease; N = normal; NS = not significant; P = prism; *P* = significance of difference from normal; PS = pulmonary stenosis; S = Simpson's rule; SD = Standard deviation; ToF = Tetralogy of Fallot; VSD = ventricula septal defect.

. *Group 3* (ventricular septal defect) had normal mean volumes with no difference found between patients with a large or small shunt or those studied before or after operation. The two patients with pulmonary arterial banding had low normal volumes.

In Group 4 (tetralogy of Fallot) the mean volumes both pre- and postoperatively were normal. One patient studied preoperatively had an end-diastolic volume more than 2 standard deviations above the normal mean value (124 ml/m^2). He did not have radiographic cardiac enlargement, but his right ventricular end-diastolic pressure was elevated for age (8.6 mm Hg). A second patient studied preoperatively had high normal end-diastolic volume (94 ml/m^2). He had moderate pulmonary insufficiency, but his end-diastolic pressure and radiographic heart size were normal. The one patient studied postoperatively with an end-diastolic volume/m^2 slightly above 2 standard deviations from the normal mean value (95 ml) had significant pulmonary insufficiency. Ejection fraction was decreased in this patient (0.36) and in one other patient studied postoperatively (0.41). In neither one was heart size increased radiographically. Two other patients studied postoperatively had an end-diastolic

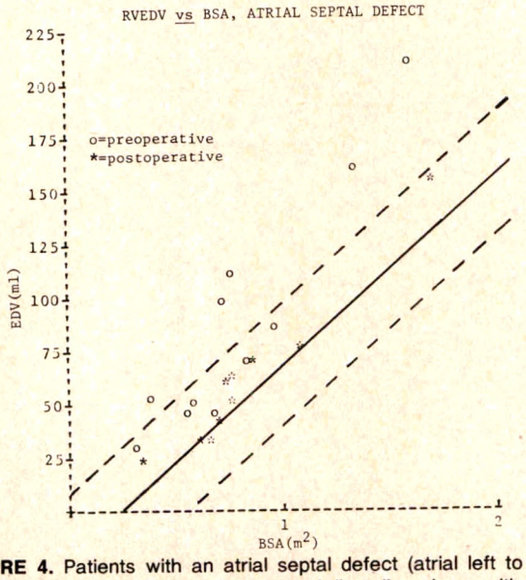

FIGURE 4. Patients with an atrial septal defect (atrial left to right shunt). Variation of right ventricular end-diastolic volume with body surface area. Conventions as in Figure 3.

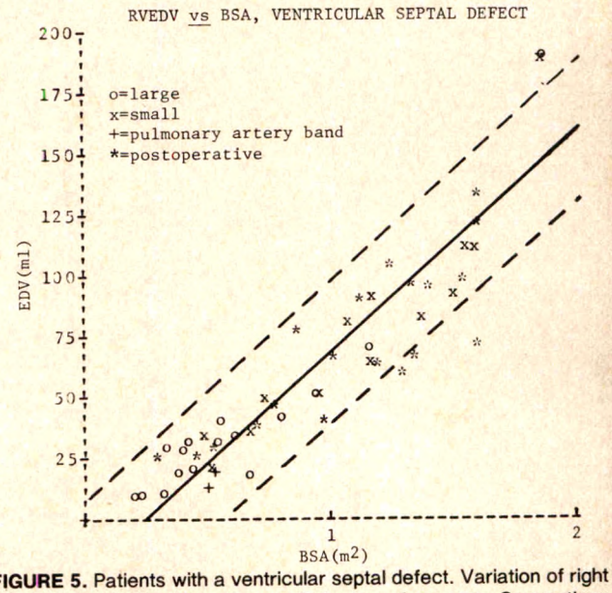

FIGURE 5. Patients with a ventricular septal defect. Variation of right ventricular end-diastolic volume with body surface area. Conventions as in Figure 3.

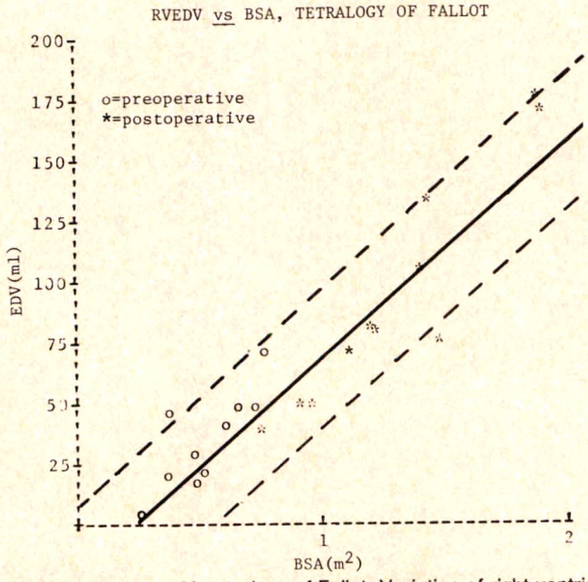

FIGURE 6. Patients with tetralogy of Fallot. Variation of right ventricular end-diastolic volume with body surface area. Conventions as in Figure 3.

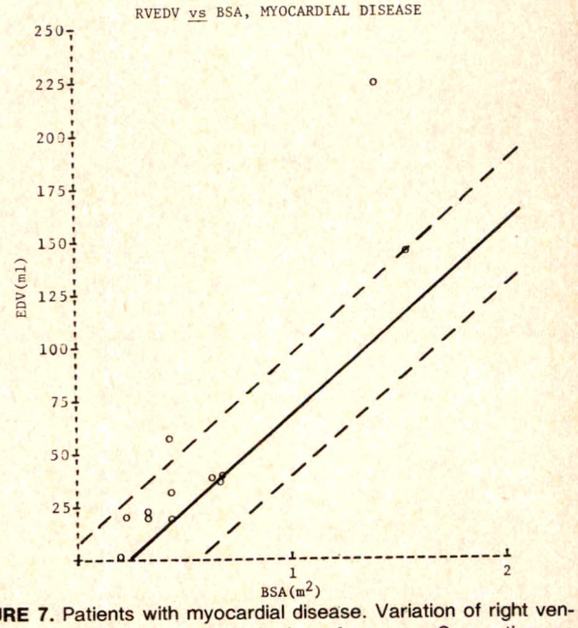

FIGURE 7. Patients with myocardial disease. Variation of right ventricular end-diastolic volume with body surface area. Conventions as in Figure 3.

volume at the upper limits of normal (94 and 91 ml/m^2, respectively). Both had moderate pulmonary insufficiency, and one had cardiac enlargement by X-ray examination.

In Group 5 (myocardial disease) mean end-diastolic volume/m^2, mean end-systolic volume/m^2 and mean ejection fraction were normal. Only two patients in this group had an end-diastolic volume more than 2 standard deviations above the normal mean value (135 and 161 ml/m^2, respectively). Right ventricular stroke volume was increased in the former patient (65 ml/m^2). That patient had a normal ejection fraction (0.52), but ejection fraction was decreased (0.34) in the other. Corresponding left ventricular values for these patients were: end-diastolic volume/m^2 203 and 219 ml, stroke index 76 and 57 ml, ejection fraction 0.37 and 0.36 and end-diastolic pressure 26 and 10 mm Hg. Cardiac output (Fick method) was 4.9 liters/min per m^2 in the second patient, and 2.9 liters/min per m^2 (with use of an assumed oxygen consumption) in the first patient. The second patient had elevated right ventricular end-diastolic pressure (10 mm Hg). Both had clinical evidence of right-sided heart failure with hepatomegaly. The first patient had massive mitral insufficiency believed to be secondary to cardiac dilatation.

Discussion

The use of an electronic planimeter linked to a programming calculator and output writer greatly facilitates the application of Simpson's rule to right ventricular volume determination. It is comparable in accuracy to the manual method, but the equipment is expensive and is not available in most laboratories. Therefore, Simpson's rule remains limited in its clinical usefulness. The prism method requires no such equipment, the measurements are easily made manually and the calculations are quite simple.

Objections to the use of a geometric model have been raised on the basis that it is less accurate than Simpson's rule. However, in a previous report[2] comparing Simpson's rule with a geometric model in right ventricular case studies, little difference was shown in *r* values between the methods. No in vivo volume data were presented. Arcilla et al.[8] and Thilenius and Arcilla[6] used a geometric model but did not compare results with Simpson's rule. Graham et al.[1] compared Simpson's rule with two geometric models, finding little difference in the cast studies; they did not present a comparison of in vivo volumes by the various methods. Our investigation indicates that a simple geometric model, a prism with a triangular base, can be compared in accuracy with Simpson's rule both in cast studies and in in vivo volume calculations.

Normal Ventricular Volumes

In comparing our right and left heart volumes we found the right ventricle to be slightly larger and to have a lower ejection fraction than the left. Other studies, one in infants and children[6] and another in adults,[2,9] have found the same relation between the right and left ventricles, but Graham et al.[1,8] did not demonstrate any such differences in their studies (Table II). Although further data are needed to clarify this issue, it appears that the right ventricle is slightly larger than the left.

Our normal data are comparable with those of previous reports,[1,6] but we failed to demonstrate significantly lower volumes in infants. However, our youngest "normal" patient was 6 months old and only 7 of the 70 patients were less than 1 year of age, whereas in Graham's study 6 patients were 5 months of age or younger and 7 of 16 in the normal group were less than 1 year of age.

After normalization of volumes for body surface area, there remained a significant positive correlation with age. This observation is in agreement with other investigators' findings of smaller volumes in young infants. Also, in this regard, Gentzler et al.[2] reported in adults with normal right heart chambers higher values than those reported by others[1,6] in children.

Abnormal Right Ventricular Volumes

Pulmonary stenosis: In contrast to Graham et al.,[1] we found a small but definite decrease in mean right ventricular volume and stroke index, plus increased ejection fraction, in patients with pulmonary stenosis. Similar changes have been reported in left ventricular volume and ejection fraction in pediatric patients with aortic stenosis.[5] The right ventricle, as well as the left, is capable of ejecting an increased fraction of its volume of blood when exposed to a chronic increase in afterload. Whether this is due to increased contractility or to muscular hypertrophy remains to be investigated. The finding of normal mean volumes and ejection fraction in postoperative patients in this group lends support to the presence of a reversible adaptation to increased afterload in these patients. The individual patient in the postoperative group with increased volume had increased preload; thus, his condition was analogous to that of patients in Group 2 (atrial left to right shunt).

Gentzler et al.[2] described only two adult patients with pulmonary stenosis, both of whom had low values for end-diastolic volume (more than 2 standard deviations below the normal mean value in one). Both had a normal ejection fraction. Whether or not long-term pressure load of the right ventricle leads to compromise of function remains to be studied.

Atrial septal defect: Demonstration of a large increase in right ventricular volume in atrial left to right shunt is in agreement with findings by Graham et al.[1] in atrial septal defect and total anomalous pulmonary venous drainage and by Gentzler et al.[2] in patients with tricuspid insufficiency and atrial septal defect. Decreased ejection fraction in the patients in the latter study may have been due to long-term volume overload (increased preload) or to coronary artery disease or myocardial disease of other causes. In the absence of other such factors the right ventricle adapts to increased preload by increased end-diastolic and end-systolic volumes as well as increased

stroke index, probably through the Starling mechanism. The finding of normal or nearly normal volumes postoperatively is evidence for a reversible adaptation to increased preload in children.

Ventricular septal defect: No data are available on in vivo right ventricular volume in ventricular septal defect in children. Gentzler et al.[2] reported findings in two adult patients with a ventricular septal defect, one of whom also had right ventricular hypertension. Right ventricular volume was increased in the latter patient and normal in the other. In our group of 34 patients ventricular septal defect did not in most cases result in volume overload of the right ventricle. It may be that the site of the defect (in our study group all moderate to large defects were subaortic) results in shunting directly from the left ventricle to the pulmonary artery without overloading the right ventricle. Patients with a large muscular ventricular septal defect might then be expected to have an enlarged right ventricle.

Tetralogy of Fallot: Patients with tetralogy of Fallot generally have normal heart size by X-ray examination, and this correlates well with our finding of normal mean right ventricular volume in this group. The lesion is a complex one and may, in the evolution of the disease, present predominantly a volume or a pressure load to the right ventricle. In general, the latter predominates and the right ventricle responds by hypertrophy but not enlargement. In the group of patients studied, right ventricular volume tended to be high normal or increased in the presence of pulmonary insufficiency, a situation resulting in increased preload.

Myocardial disease: Our finding of normal mean right ventricular volume in patients with myocardial disease is in accord with similar findings by Gentzler et al.[2] in 7 of 13 patients with myocardial compromise. It is also in agreement with clinical and pathologic evidence that myocardial disease affects primarily the left side of the heart. Since cardiac output was measured in only four of these patients it cannot be stated whether or not decreased cardiac output and then decreased preload to the right ventricle resulted in normal right ventricular volume. However, the finding of normal or increased right ventricular stroke volume is evidence against this premise.

In summary, we have shown that a simple geometric model can be used to determine angiographic right ventricular volume with accuracy and that the results correlate well with those obtained utilizing Simpson's rule. The normal right ventricle is slightly larger than the left and has a lower ejection fraction. In chronic pressure load or increased afterload, the right ventricle tends to be smaller than normal and ejection fraction is increased. In chronic volume load or increased preload it is larger than normal but has a normal ejection fraction. In ventricular septal defect, tetralogy of Fallot and myocardial disease, the right ventricle is generally normal in size.

Acknowledgment

We gratefully acknowledge the assistance of Dr. F. A. O. Eckner in preparation of the casts. We also thank Mr. Frank Domanszky, Ms. Audra Jarasius, Ms. Marilyn Williams and Mr. William Johnson for expert technical assistance.

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Advances in Clinical Vectorcardiography

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With use of the Frank lead system, still loop and timed vectorcardiograms were recorded in more than 5,000 patients subjected to complete right and left heart catheterization and selective coronary cineangiography. Data so obtained demonstrated clinical superiority of the vectorcardiogram over the standard 12 lead scalar electrocardiogram. Specific advantages of the vectorcardiogram include (1) recognition of undetected atrial and ventricular hypertrophy, (2) greater sensitivity in identification of myocardial infarction, and (3) superior capability for diagnosis of multiple infarctions in the presence of fascicular and bundle branch blocks. The timed biplane vectorcardiogram is as useful as any number of simultaneously recorded electrocardiographic leads for the analysis of complex arrhythmias and beat to beat changes in intraventricular conduction. Since the validity and usefulness of this technique have been established, it should become part of the routine noninvasive evaluation of patients with cardiovascular disorders.

Recent discussion at national scientific meetings and examination of current publications in cardiology indicate a resurgence of activity in the field of clinical vectorcardiography. The advent of aortocoronary bypass surgery has provided a major stimulus for such investigation, and papers have appeared describing the influence of cardiac revascularization on the vectorcardiogram.[1–3] Closely linked to these operative interventions has been the widespread application of cardiac catheterization and selective coronary arteriography. Prior to 1960 the diagnostic value of vectorcardiography could be validated only by postmortem examination. Fortunately, it is now possible to evaluate merits of the technique by correlation with angiographic and hemodynamic findings in living subjects. During the past 10 years we have had the opportunity of examining this correlation in more than 5,000 subjects with a variety of cardiac abnormalities.

The purpose of this paper is to review recent advances in clinical vectorcardiography. Furthermore, specific advantages of the vectorcardiogram over the standard scalar electrocardiogram will be discussed.

Vectorcardiographic Lead Systems

The multiplicity of lead systems has been a source of consternation to both neophytes and experienced vectorcardiographers. Ideally, the clinician or beginner might peruse basic papers relating to each method and thereby decide on the lead system of his choice. Unfortunately, he would encounter a maze of theoretical equations based on cube, triangle, parallelogram or tetrahedron torso projections.[4] Physicists notwithstanding, this confrontation could discourage even the most aggressive initiate, who might withdraw from vectorcardiography altogether. During the past 5 years, the literature on this subject, as well as discussion at postgraduate courses in basic and advanced vectorcardiography, has indicated that more than 85 percent of those interested in the technique utilize the Frank lead system. No investigator has demonstrated the *clinical* superiority of any other lead system and, with the

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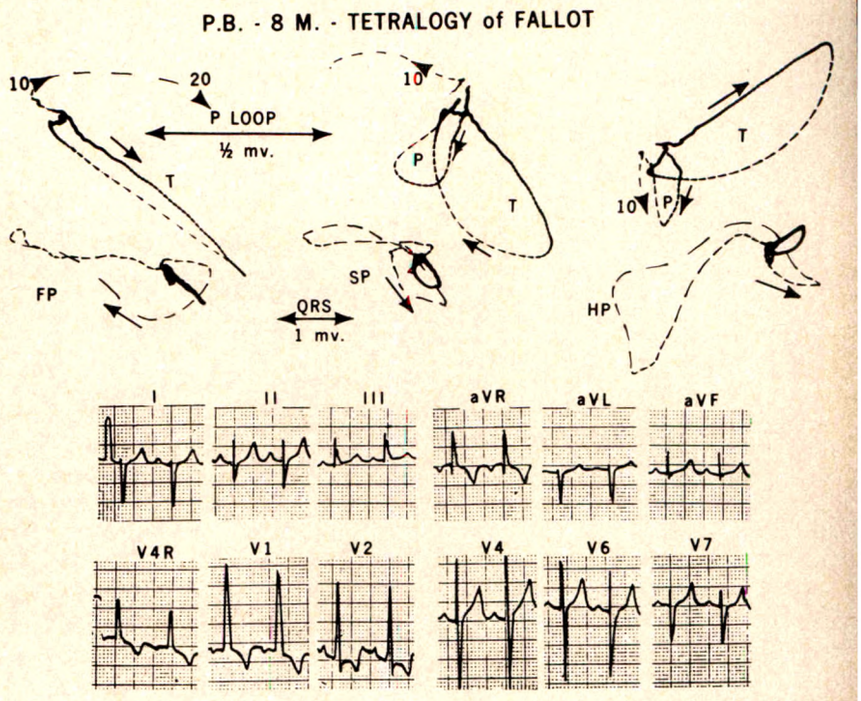

FIGURE 1. Vectorcardiogram and electrocardiogram from an 8 year old boy with tetralogy of Fallot. Note the inverted P wave in scalar lead V_1. Left sagittal plane (SP) and horizontal plane (HP) P loops are directed entirely anteriorly, diagnostic of right atrial enlargement. Large rightward directed QRS vector forces indicate right ventricular hypertrophy. FP = frontal plane.

thought of uniformity in mind, it is suggested that the Frank technique be adopted for use in all clinical vectorcardiographic laboratories. Interestingly, "majority rule" applies to electrocardiography, where the basic 12 lead tracing is generally accepted worldwide despite practical advantages of high lateral and posterior unipolar recordings. The laudable goal of uniformity[4] dictates that the most widely utilized system be applied for clinical vectorcardiograms, regardless of theoretical reservations concerning instability of the trielectrode technique for recording the horizontal plane forces.[5]

The frontal, left sagittal and horizontal plane Frank vectorcardiograms[6] described here were recorded with subjects in the supine position. The fourth intercostal space was used for placement of the chest electrodes.[7] All vectorcardiograms were recorded on a DR-8 Electronics for Medicine oscilloscopic photographic recorder using a vectorcardiographic channel. Still and timed vectorcardiograms[8,9] ("running loops") were magnified to provide better analysis of the P loop together with the initial and terminal components of the QRS loop. The loops were interrupted at 2 msec intervals.

Atrial Hypertrophy

Analysis of the vectorcardiographic P loop is clearly superior to the 12 lead electrocardiogram for the diagnosis of right, left and biatrial hypertrophy. Selvester and Haywood[10] found the timed vectorcardiogram more than three times as sensitive as the conventional electrocardiogram in detecting atrial abnormalities defined by conventional criteria. It is not widely appreciated that a large negative P wave deflection in lead V_1 is, under certain conditions, a sign of *right* and not of left atrial hypertrophy. In such cases the vectorcardiographic P loop may be directed entirely anteriorly and thus be diagnostic of right atrial hypertrophy. Examination of the P loop configuration demonstrates that the vast majority of the P loop area is projected on the negative side of the V_1 perpendicular, thus accounting for inverted P waves in this lead (Fig. 1). The absence of an inverted P wave in lead V_1 in association with low amplitude P waves of increased duration in the standard and augmented leads may render the electrocardiographic differential diagnosis of left atrial hypertrophy and intraatrial conduction defect quite difficult. In such cases the vectorcardiogram provides a definitive means of diagnosis. P loops of prolonged duration with major posteriorly oriented vector voltage indicate left atrial enlargement under these conditions (Fig. 2).

Ventricular Hypertrophy

Right ventricular hypertrophy: Numerous carefully performed studies have demonstrated superiority of the vectorcardiogram for the diagnosis of right ventricular hypertrophy. Hamer[11] concluded that the vectorcardiogram was more successful than the electrocardiogram in recognition of right ventricular hypertrophy in patients with mitral valve disease. Major diagnostic rightward directed QRS vector forces are frequently observed in the vectorcardiograms of subjects with mitral stenosis, pulmonary hypertension and borderline findings on scalar electrocardiograms (Fig. 3). With use of quantitative measurements, it has been ascertained that the vectorcardiogram is a reliable method for predicting right ventricular pressures in groups of patients with atrial septal defect,[12] pulmonary stenosis,[13] pulmonary heart disease and mitral stenosis.[14] Liebman et al.[15] noted that the Frank vectorcardiogram provided an excellent means of predicting normal versus abnormal pulmonary function tests in subjects with cystic fibrosis. Furthermore, it was demonstrated that the standard electrocardiogram was not as accurate as the Frank vectorcardiogram in this clinical setting.

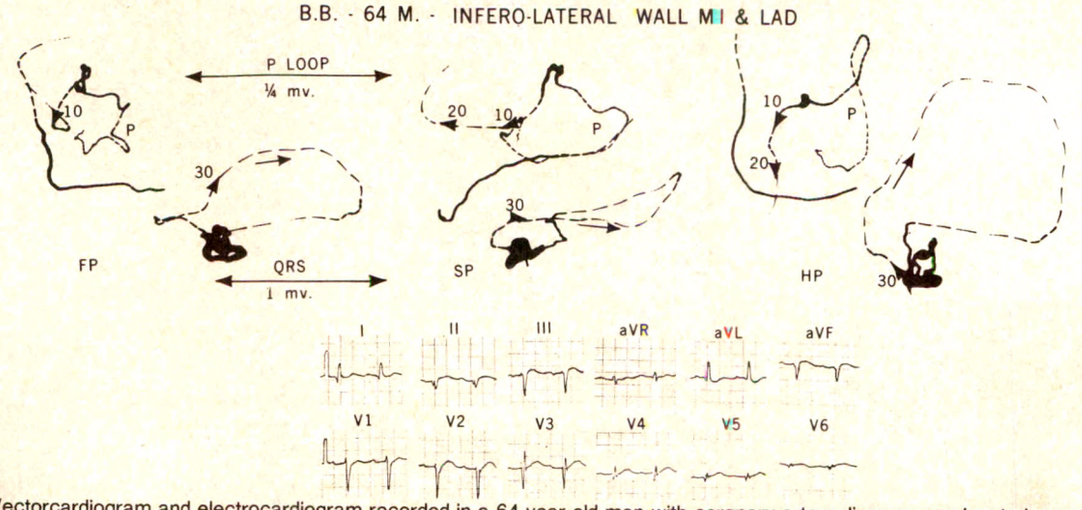

FIGURE 2. Vectorcardiogram and electrocardiogram recorded in a 64 year old man with coronary artery disease, an elevated mean pulmonary arterial "wedge" pressure and left atrial enlargement. The electrocardiogram shows low amplitude P waves of 0.12 second duration. The P wave in scalar lead V_1 is predominantly upright. P loop vectorcardiograms demonstrate large leftward and posteriorly directed forces with a 0.20 mv maximal P loop deflection vector in the horizontal plane. These findings are diagnostic of left atrial hypertrophy. There is associated electrovectorcardiographic evidence of an inferolateral wall myocardial infarction (MI) and abnormal frontal plane left axis deviation (LAD).

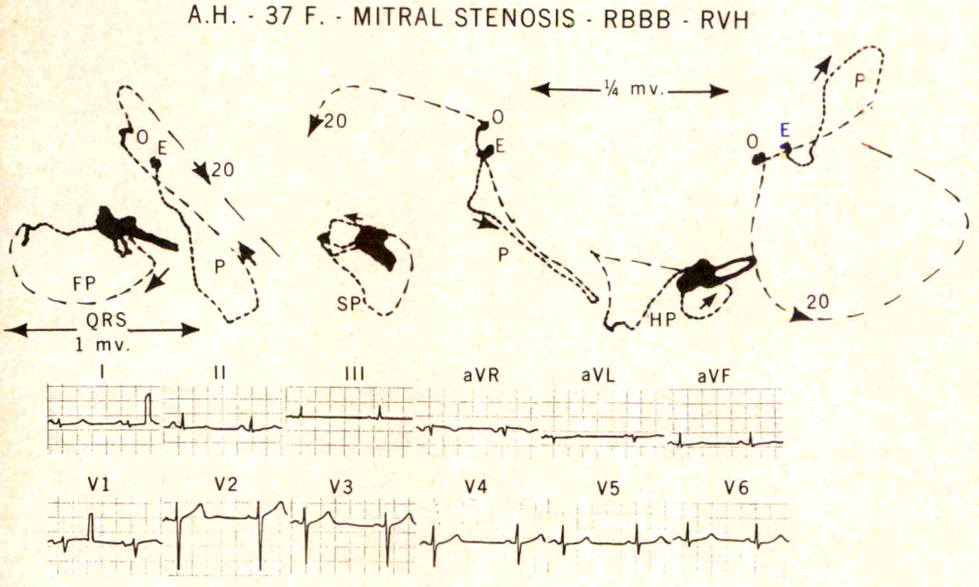

FIGURE 3. Vectorcardiogram and electrocardiogram from a 37 year old woman with mitral stenosis and pulmonary hypertension. The vectorcardiogram shows large posteriorly and leftward directed P loop voltage with major frontal plane and horizontal plane rightward oriented QRS forces. The QRS duration is 118 msec. A terminal delay in inscription of the QRS vectors suggests right bundle branch block (RBBB). These findings are diagnostic of left atrial and right ventricular enlargement (RVH), which were noted at cardiac catheterization. The scalar electrocardiogram demonstrates minor P wave notching and S waves in leads I, aVL, aVF and V_4 to V_6. Such electrocardiographic findings are nondiagnostic and frequently noted in normal women under the age of 40 years.

Some of the most striking discrepancies between vectorcardiographic and electrocardiographic interpretation are seen during the involutionary stages of right ventricular hypertrophy. The Frank vectorcardiogram has been shown to be a more sensitive technique for assessing such changes[16] (Fig. 4). Electrocardiograms in patients with diagnostic type "B" patterns of right ventricular hypertrophy in horizontal plane vectorcardiograms frequently show normal findings and are notoriously inaccurate in predicting right heart pressures.

Hamby et al.[17] found the analysis of Frank vectorcardiograms useful in distinguishing T loop abnormalities arising as a consequence of right ventricular hypertrophy from those related to ischemic heart disease. The absence of uncomplicated dextrocardia in an otherwise healthy adult patient with vectorcardiographic features of severe right ventricular hypertrophy should bring to mind the diagnosis of congenital complete defect of the left pericardium[18] (Fig. 5). Rotational and right heart mass displacement effects may produce these unusual vectorcardiographic findings, which are still incompletely understood.

Left ventricular hypertrophy: The diagnosis of left ventricular hypertrophy is facilitated by vectorcardiography, especially when there is coexisting myocardial infarction. Attenuation of leftward-directed forces by myocardial infarction may render the electrocardiographic diagnosis of left ventricular hypertrophy difficult. Under these conditions, the presence of posteriorly directed QRS forces of greater than 2.2 mv in the horizontal plane vectorcardiogram

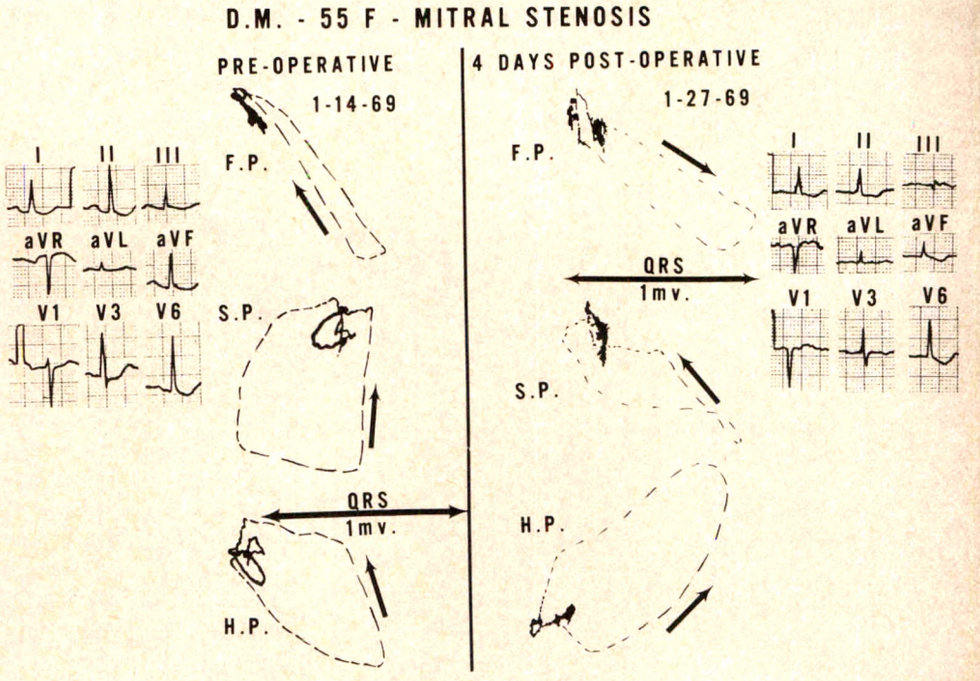

FIGURE 4. Preoperative and postoperative vectorcardiograms and electrocardiograms from a 55 year old woman with mitral stenosis. The preoperative vectorcardiogram shows counterclockwise rotation of the horizontal plane QRS loop with major anteriorly directed forces (type "B" right ventricular hypertrophy). The preoperative pulmonary arterial pressure was 50 mm Hg. Four days after mitral valve replacement the horizontal plane QRS loop is normally directed to the left and posteriorly. There are no significant differences between the preoperative and postoperative electrocardiograms. Furthermore, neither electrocardiogram suggests right ventricular hypertrophy. (Reproduced with permission.[58])

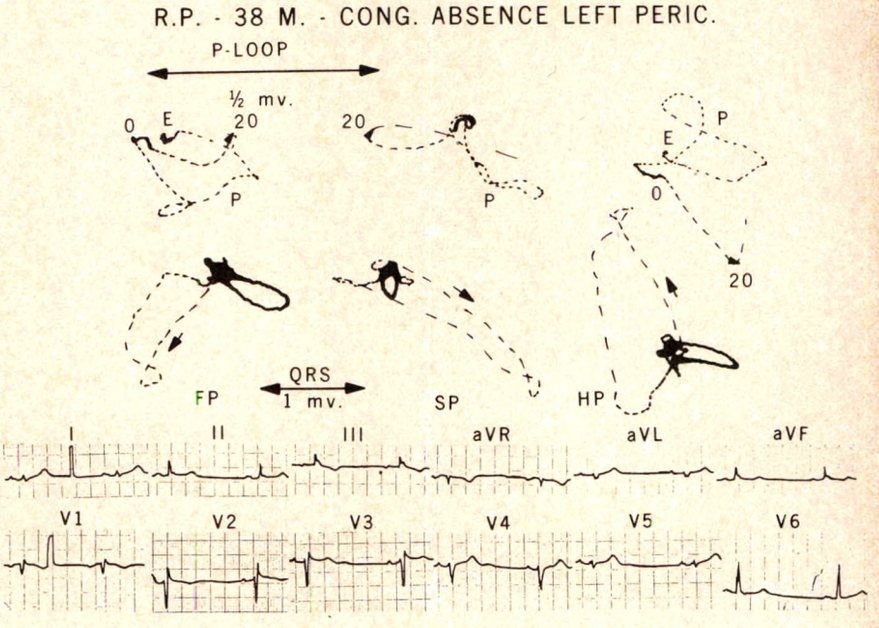

FIGURE 5. Vectorcardiogram and electrocardiogram recorded in a 38 year old man with congenital (CONG.) complete absence of the left pericardium (PERIC.) and no catheterization evidence of coronary, valvular or myocardial disease. The vectorcardiogram shows marked displacement of the QRS vectors to the right, with predominant counterclockwise rotation of the horizontal plane QRS loop. These findings simulate type "C" right ventricular hypertrophy.

is virtually diagnostic of underlying left ventricular hypertrophy. Roberts and Fowler[19] published data indicating utility of the Frank vectorcardiogram for serially estimating left ventricular pressure in established cases of transposition of the great arteries.

Electrovectorcardiographic tracings diagnostic of left ventricular hypertrophy and "strain" have been described in well conditioned athletes[20] with no catheterization evidence of heart disease. Whether such changes revert to the "normal" limits of measurement with more sedentary activity is currently unknown.

Biventricular hypertrophy: Varriale et al.[21] reported distinctive qualitative and quantitative features in the horizontal plane Frank QRS loop in two thirds of patients with clinical, hemodynamic and surgical evidence of biventricular hypertrophy. These changes consisted of abnormal posterior vector displacement and counterclockwise inscription along with an S loop of significant duration and magnitude. The frontal plane QRS loop provides additional evidence for right ventricular hypertrophy when the maximal QRS vector is directed toward the right and rotates in a clockwise fashion.

Coronary Artery Disease and Myocardial Infarction

McConahay et al.[22] performed an extremely well designed study on comparative quantitative analysis of the electrocardiogram and Frank vectorcardiogram in subjects with coronary artery disease. Correlations with the coronary arteriogram and left ventriculogram demonstrated that analysis of the quantitative vectorcardiogram was superior to the usual electrocardiographic analysis in the accurate detection of myocardial infarction. Detailed descriptions of the electrocardiographic and vectorcardiographic criteria required for diagnosis were presented, distinguishing this paper from many others on the subject. Maron et al.[23] found the vectorcardiogram to be a useful clinical tool for the diagnosis of significant coronary artery disease and large myocardial infarcts. Interestingly, there was no close correlation between the presence of smaller vector loop "bites" (0.08 to 0.13 mv, 4 to 6 msec) and angiographic data. In our experience the vectorcardiogram has proved to be a very accurate technique for diagnosing myocardial infarction.

Anterior infarction: In the absence of complete left bundle branch block, a posteriorly oriented 20 msec QRS vector is predictive of anterior wall myocardial fibrosis in more than 95 percent of cases (Fig. 6). The term fibrosis is specifically used to denote that coronary artery disease is but a single cause of fibrotic and poorly contracting myocardial segments. Valvular heart disease along with primary and secondary cardiomyopathies can also result in posteriorly[24] or superiorly oriented initial QRS vector forces. In such cases there is usually a substantial myocardial component contributing to the patient's disability. Care must be taken to obtain high resolution and magnification of initial QRS vector loop forces so that spurious diagnoses of myocardial fibrosis are not made (Fig. 7). On occasion, the direct light beam writing instrument has revealed preservation of initial anterior QRS forces that were obscured by P-T vectors on a camera-oscilloscopic device.

Inferior or lateral infarction: During hyperacute stages of myocardial infarction, the vectorcardiogram frequently reveals characteristic alterations

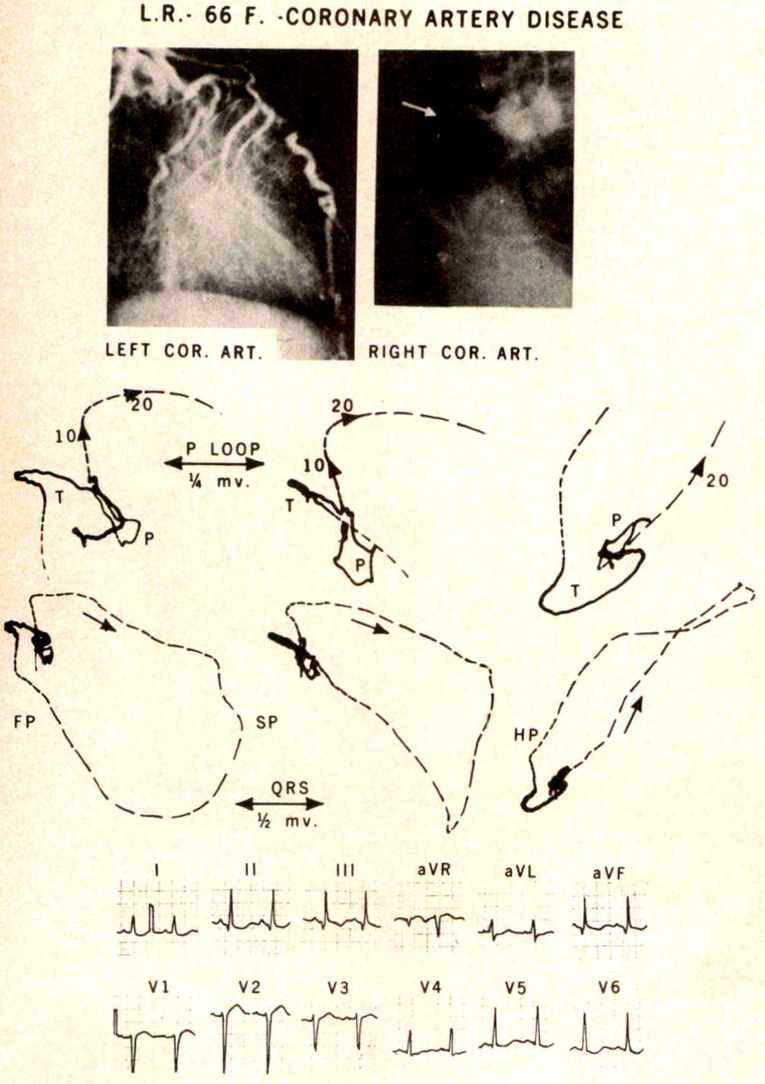

FIGURE 6. Selective coronary arteriograms, vectorcardiogram and electrocardiogram in a 66 year old woman with coronary artery disease. The coronary arteriograms demonstrate multiple obstructive lesions ranging from 80 to 95 percent stenosis in the right, left anterior descending and left circumflex vessels. The vectorcardiogram shows superiorly and posteriorly directed 25 msec QRS vectors diagnostic of, respectively, inferior and anteroseptal wall myocardial infarction. The scalar electrocardiogram demonstrates Q waves in leads II, III and aVF diagnostic of old inferior wall infarction. There is no electrocardiographic evidence of anteroseptal wall myocardial infarction. COR. ART. = coronary artery.

indicating major myocardial destruction at a time when the electrocardiogram shows tall and peaked T waves[25] alone. This advantage of the vectorcardiogram is particularly evident in the case of acute inferior[26] or lateral wall infarction (Fig. 8). When definite initial QRS vector (20 to 30 msec) criteria for inferior wall infarction are not met, there may be characteristic mid to late changes in the frontal plane QRS loop that suggest the correct diagnosis.[27] These alterations consist of large "bites" or unexpected directional deviations of the terminal QRS forces (Fig. 9).

Posterior infarction: The vectorcardiogram is overwhelmingly more sensitive than the electrocardiogram in establishing the diagnosis of posterior wall left ventricular infarction.[28,29] Gray et al.[30] examined the coronary angiograms of 31 patients with vectorcardiographic features of posterior wall myocardial infarction. Of 31 patients with diagnostic loops, 25 had associated coronary disease. Only 6 of the 31 patients had electrocardiographic evidence of posterior wall myocardial infarction. When the scalar electrocardiogram shows unequivocal evidence of an inferior wall infarction, the presence of a dominant R wave in lead V_1 or possibly V_2 strongly suggests coexisting posterior wall damage. On the other hand, there are no well established criteria for infarction based on an isolated R/S ratio greater than 1 in lead V_2 of an otherwise normal-appearing electrocardiogram (Fig. 10). Right ventricular hypertrophy represents a major problem in the electrovectorcardiographic differential diagnosis of posterior wall myocardial infarction. Mathur and Levine[31] found the magnitude of terminal rightward voltage less than 1.0 mv in 88 percent of 85 patients with posterior wall myocardial infarc-

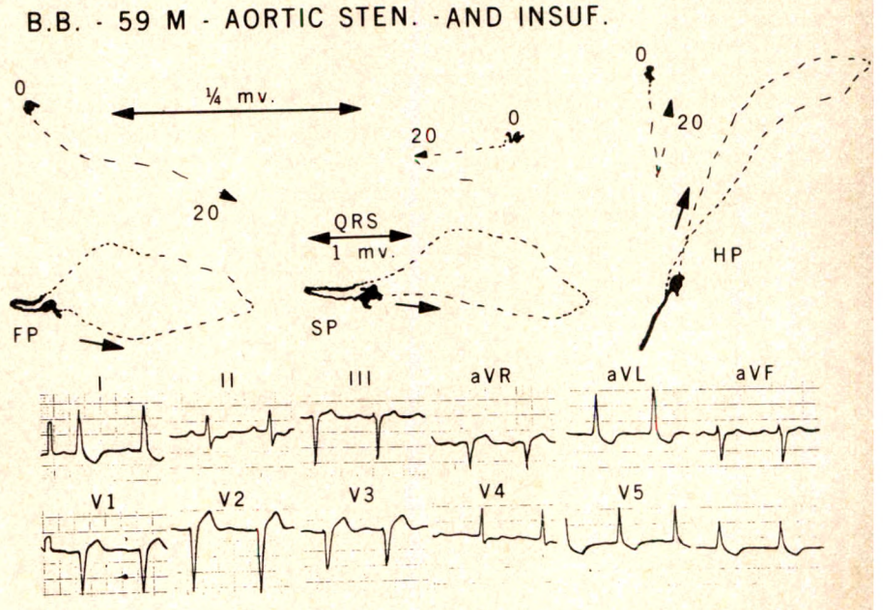

FIGURE 7. Vectorcardiogram and electrocardiogram in a 59 year old man with normal coronary arteries and combined aortic stenosis (STEN.) and insufficiency (INSUF.). At the standard magnification, initial 20 msec QRS vectors are obscured at the E-0 points in the sagittal and horizontal planes. A greater magnification of the early QRS loop indicates preservation of anterior 20 msec QRS vector forces. There is associated left ventricular hypertrophy. The electrocardiogram reveals poor progression of R waves in leads V_1 through V_3 together with evidence of left ventricular hypertrophy and "strain."

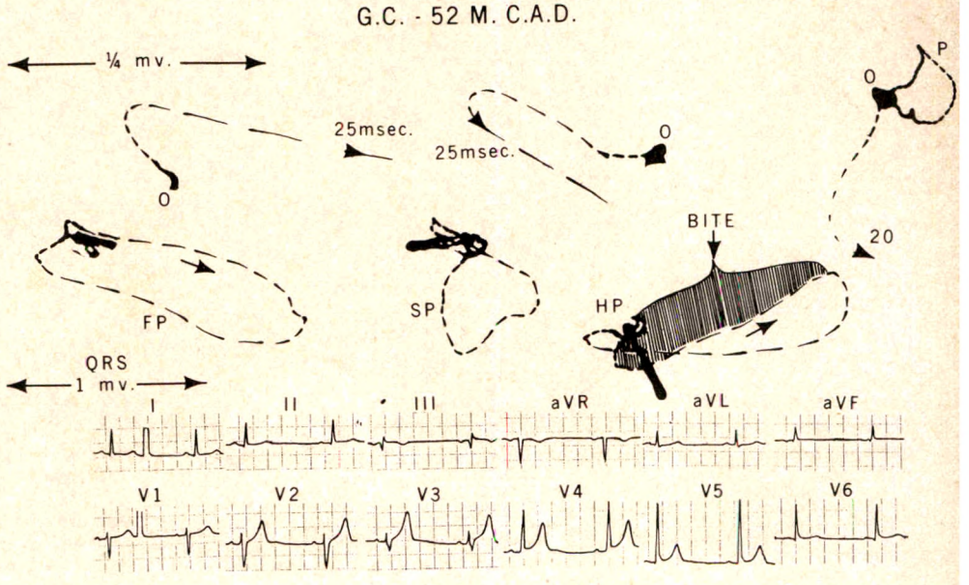

FIGURE 8. Vectorcardiogram and electrocardiogram recorded during the hyperacute stages of anterior wall myocardial infarction in a 52 year old man with coronary artery disease (C.A.D.). The frontal plane and sagittal plane initial 25 msec QRS vectors are directed superiorly and thus diagnostic of inferior wall infarction. Note the extensive "bite" in the horizontal plane QRS loop, indicating loss of left ventricular mass. The electrocardiogram shows S-T segment elevation and peaking of T waves in precordial leads V_2 through V_5.

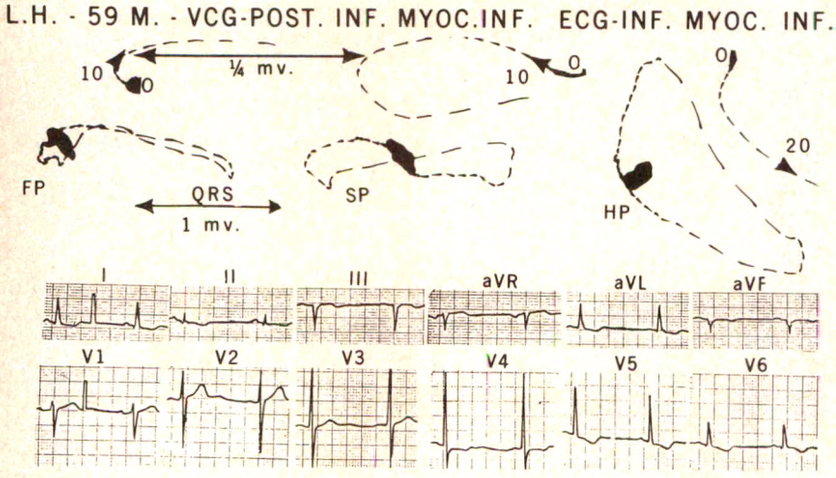

FIGURE 9. Vectorcardiogram (VCG) and electrocardiogram (ECG) from a 59 year old man with diffuse triple vessel coronary artery disease and complete occlusion of the right coronary artery. The initial 24 msec vectors in the frontal plane QRS loop are directed superiorly. The terminal QRS vector forces unexpectedly course in a superior direction, resulting in an inferior QRS loop "bite." The initial 48 msec QRS vectors are oriented anteriorly in the horizontal plane and are thus diagnostic of posterior wall myocardial infarction (MYOC. INF.). There are large QS complexes in scalar leads III and aVF with no electrocardiographic evidence of posterior wall infarction. INF. = inferior; POST. INF. = posteroinferior.

tion. In addition, horizontal plane right axis deviation was unusual in such cases. Concordant direction of the QRS-T loop maximal deflection vectors in the horizontal plane has also been considered to be suggestive of posterior wall infarction.[28] Taken together, all of these findings can still be misleading in the individual case. Type B right ventricular hypertrophy, usually associated with mild to moderate pulmonary hypertension, can result in vectorcardiographic features identical with those seen in posterior wall infarction.[28]

Analysis of T vector: Quantitative and morphologic analysis of the T vector loop has added a new dimension to the detection of underlying coronary artery disease.[32] Gray and Bell[33] compared the resting and postexercise electrocardiograms and vectorcardiograms in 100 patients who underwent selective coronary angiography. Utilizing a Frank frontal or horizontal plane T loop length/width ratio of 2.6 or less or an increase in the S-T segment opening of 0.1 mv or more as ischemic responses, they found that the vectorcardiogram correlated with the presence of severe coronary artery disease in 81 percent of cases. A 1 mm flat electrocardiographic S-T segment depression was found in only 35 of 59 patients (59 percent). In general, clockwise rotation of the T loop in the horizontal plane is indicative of heart disease[34] and may help elucidate the significance of inverted T waves in the right precordial electrocardiographic leads ("juvenile pattern") of patients with questionable or borderline physical findings and history.

Differentiation from hypertrophic cardiomyopathy: Idiopathic hypertrophic subaortic stenosis results in vectorcardiographic changes that are notoriously difficult to distinguish from these of myocardial infarction[35,36] (Fig. 11). Rothfeld and Zucker[37] suggested that the large rightward septal forces associated with hypertrophic subaortic stenosis could be differentiated from those of true myocardial infarction. They observed significant irregular and delayed inscription of the initial QRS vectors when true myocardial infarction was operative. Unfortunately, lateral wall myocardial infarction can also produce uniform inscription of the initial QRS vector forces.

Conduction Abnormalities

Left anterior hemiblock: Distinctive vectorcardiographic patterns compatible with theoretical and experimental models of unifascicular block have emerged within the last decade. Left anterior fascicular block results in preferential initial depolarization of the inferior myocardium. Frontal plane 10 to 20 msec QRS vectors are therefore directed inferiorly and to the right or left.[38–41] The balance of the frontal plane QRS loop courses in a superior direction with counterclockwise rotation and delayed inscription of the terminal 40 msec QRS vectors. Abnormal leftward directed frontal plane maximal QRS deflection vectors arise as a consequence of delayed depolarization of the superior aspect of the left ventricle. During 1971 and 1972, a series of publications appeared that shed new light on certain confusing electrocardiographic patterns of abnormal left axis deviation. Three groups of investigators,[42–45] working independently, set forth vectorcardiographic criteria for the diagnosis of coexisting left anterior hemiblock and inferior wall myocardial infarction. The features most useful for recognition of this entity are clockwise and superior inscription of the initial 20 to 30 msec QRS vectors secondary to inferior wall infarction followed by counterclockwise and delayed inscription of the terminal 40 msec QRS vectors in a superiorly displaced frontal plane loop. Kulbertus et al.[42] validated these criteria by artificially creating left anterior hemiblock aberrancy in subjects with established inferior wall infarction. Combined inferior wall infarction and left anterior hemiblock may be manifested in the electrocardiogram by rS or QS complexes in leads II, III and aVF. The rS pattern does not permit recognition of inferior infarction and a QS complex may be seen in the presence of a completely clockwise frontal plane QRS loop of uncomplicated diaphragmatic infarction. Under these conditions the vectorcardiogram provides a superior method of diagnosis (Fig. 12).

Left posterior hemiblock: This conduction defect produces preferential early depolarization of the superior aspect of the left ventricle, thereby producing

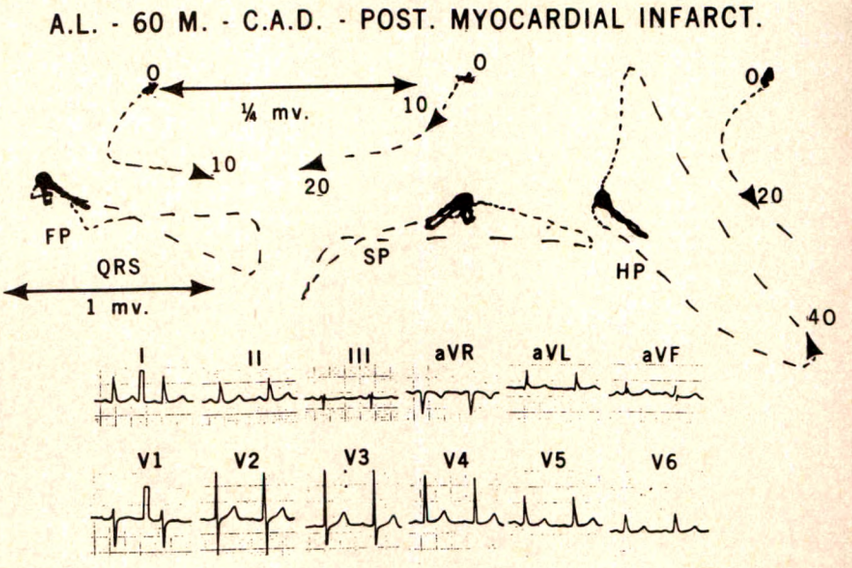

FIGURE 10. Vectorcardiogram and electrocardiogram in a 60 year old man with documented right coronary artery disease (C.A.D.) The horizontal plane vectorcardiogram shows anteriorly displaced initial 46 msec QRS vectors. More than 50 percent of the horizontal plane QRS loop area is anterior to the X axis, a finding diagnostic of posterior (POST.) wall myocardial infarction. There is a tall R wave in scalar lead V_2, but the electrocardiogram is within the normal limits of conventional criteria.

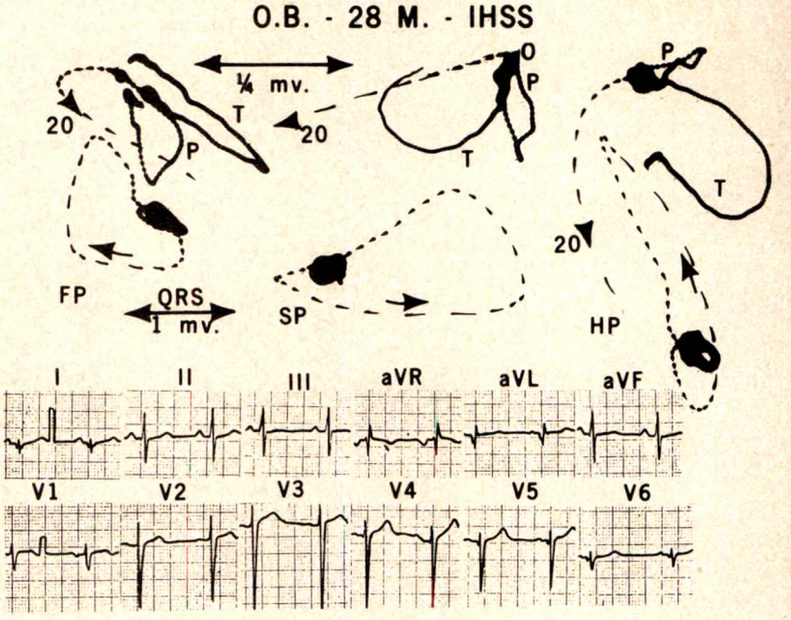

FIGURE 11. Vectorcardiogram and electrocardiogram in a 28 year old man with idiopathic hypertrophic subaortic stenosis (IHSS) and normal coronary arteries. There are electrovectorcardiographic features of lateral wall myocardial infarction and left ventricular hypertrophy. In addition, the vectorcardiogram shows major posteriorly and leftward directed P loop forces, compatible with left atrial hypertrophy. The frontal plane QRS axis in the electrocardiogram is indeterminate whereas the maximal QRS deflection vector in the frontal plane vectorcardiogram is oriented to the right and superiorly.

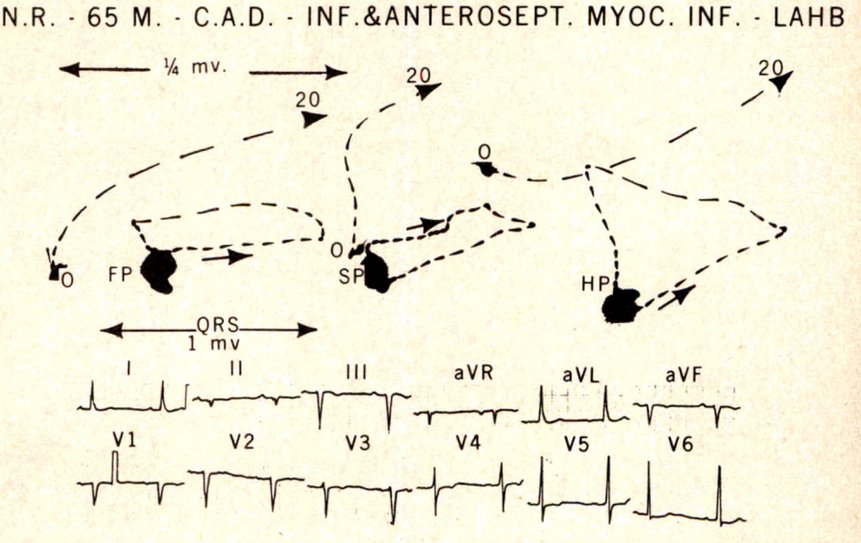

FIGURE 12. Vectorcardiogram and electrocardiogram in a 65 year old man with coronary artery disease (C.A.D.) and documented inferior (INF.) and anteroseptal (ANTEROSEPT.) wall myocardial infarctions. The frontal plane initial 20 msec QRS vectors rotate in a clockwise fashion and are displaced superiorly, a finding diagnostic of inferior wall infarction. The terminal QRS forces rotate in a counterclockwise manner with terminal delay, indicating coexisting left anterior hemiblock (LAHB). Horizontal plane initial 20 msec QRS vectors are directed posteriorly as a result of anteroseptal myocardial infarction. The electrocardiogram shows small r waves in leads III, aVF and V_2. There is abnormal left axis deviation. These small r waves do not permit satisfactory electrocardiographic diagnosis of either inferior or anteroseptal wall myocardial infarction.

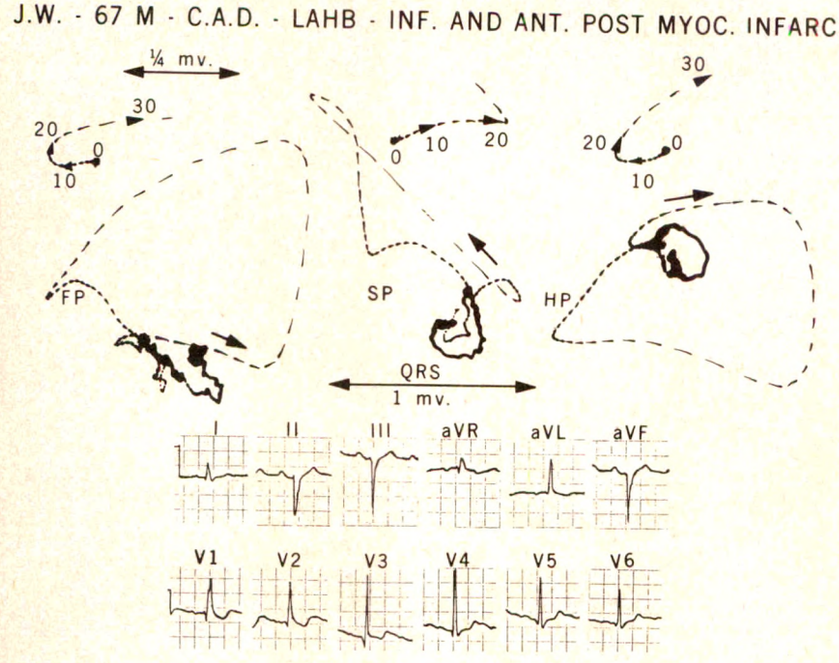

FIGURE 13. Vectorcardiogram and electrocardiogram in a 67 year old man with coronary artery disease (C.A.D.), left anterior hemiblock (LAHB) and complete right bundle branch block. The frontal plane initial 32 msec QRS vectors rotate clockwise and are directed superiorly, a finding diagnostic of inferior wall myocardial infarction. In the horizontal plane, initial 25 msec QRS forces are oriented posteriorly, indicating an anterior (ANT.) wall myocardial infarction. Complete clockwise rotation and major anterior displacement of the horizontal plane QRS loop are suggestive but not diagnostic of posterior wall infarction. The electrocardiogram shows Q waves in leads V_2 through V_6 and rS complexes in leads II and III.

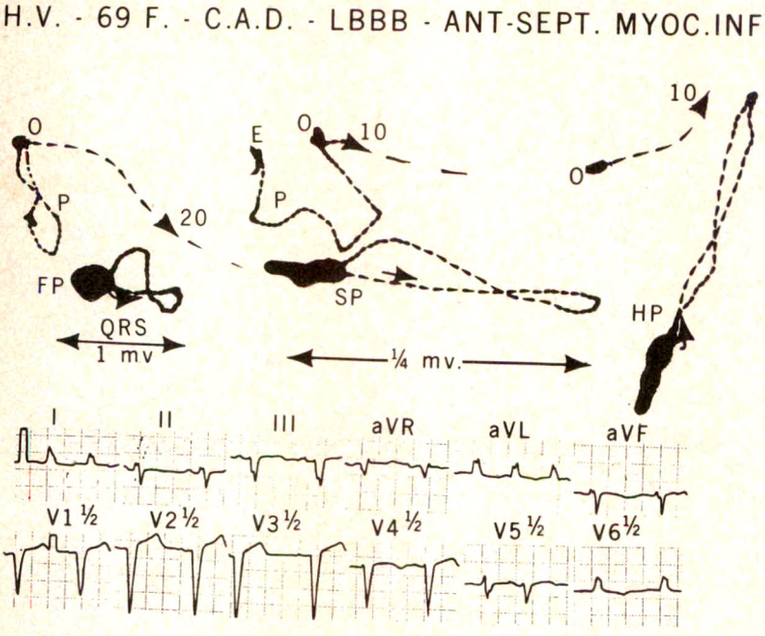

FIGURE 14. Vectorcardiogram and electrocardiogram in a 69 year old woman with documented triple vessel coronary artery disease and anterior wall dyskinesis. The vectorcardiogram and electrocardiogram reveal left bundle branch block (LBBB). Horizontal plane and sagittal plane initial 10 msec QRS vectors are directed posteriorly and thus diagnostic of anterior wall myocardial infarction.

superiorly directed 10 to 20 msec QRS vectors.[46,47] Delayed activation of the inferior wall results in clockwise rotation and right axis deviation of the frontal plane QRS loop. When left posterior hemiblock occurs in conjunction with inferior wall myocardial infarction, the Q waves in scalar leads II, III and aVF may appear small in relation to the tall R waves that follow.[48] In such cases, the initial 30 msec QRS vectors will be directed superiorly, suggesting inferior wall infarction. We have observed diminution of the Q wave voltage over a 1 year period in subjects with these combined abnormalities. It is possible that transient or altering degrees of left posterior fascicular block account for these changes, and further investigation of this phenomenon is warranted. Gaum et al.[49] reported distinctive rightward and inferiorly directed QRS vector loops in patients with supravalvular aortic stenosis and aortic coarctation. They postulated that this vectorcardiographic pattern might be attributable to selective posterobasal left ventricular hypertrophy or left posterior hemiblock.

Fernandez et al.[50] recorded Frank vectorcardiograms in patients undergoing selective coronary arteriography. Left coronary arteriography resulted in frontal plane QRS loop alterations similar to those described for left anterior hemiblock. Right coronary arteriography produced configurations of left posteri-

or hemiblock. In subjects with initial QRS vector changes of myocardial infarction, terminal QRS loop changes compatible with associated fascicular block developed. These angiographically induced QRS loop changes may be based on "peripheral" rather than isolated unifascicular block since there are usually no initial QRS vector shifts in patients without associated infarction.

Bifascicular block: The vectorcardiographic manifestations of bifascicular block[51] have recently been described in detail.[52–56] Left anterior hemiblock combined with complete right bundle branch block results in a more superior frontal plane maximal QRS vector than does isolated right bundle branch block or left anterior hemiblock.[52] It has been noted that a significant number of subjects with electrovectorcardiographic features of combined left fascicular and right bundle branch block manifest anteriorly directed or clockwise rotating horizontal plane QRS loops.[52] These major anterior vector forces may be based on (1) preferential initial posterior left ventricular wall depolarization, (2) coexisting posterior wall myocardial infarction, (3) associated right ventricular hypertrophy, or (4) more advanced "degree" of left fascicular and complete right bundle branch block. Kulbertus et al.[53] hypothesized that gradation from posterior to anterior horizontal plane QRS direction might indicate progressive damage to the conduction system. Cerqueira-Gomes et al.[55] observed that complete atrioventricular block had a greater tendency (75 percent) to occur in patients with anteriorly directed horizontal plane QRS loops. Furthermore, they could not predict the horizontal plane maximal QRS vector by examination of the 12 lead electrocardiogram. Lichstein et al.[56] concluded that the relation of horizontal plane QRS configuration to clinical course was not close enough to predict the course of an individual patient or aid in clinical management. Variance in such studies may be based on differences in underlying cause of the bilateral bundle branch block, which cannot be ascertained by examination of these papers. When left anterior hemiblock and complete right bundle branch block coexist with myocardial infarction, the vectorcardiogram is an elegant method of diagnosis (Fig. 13).

Left bundle branch block: When left bundle branch block is operative, the vectorcardiogram affords a method whereby coexisting myocardial infarction may be detected. The most reliable criteria for diagnosis of these combined abnormalities include a shift of horizontal plane QRS loop rotation from figure of eight to clockwise[57] and posterior orientation of the initial 10 msec QRS vectors[58] (Fig. 14).

Cardiac Arrhythmias

Timed vectorcardiogram: The timed vectorcardiogram ("running loop") is as useful as the scalar electrocardiogram in the surface analysis of cardiac arrhythmias.[9,58] All previously mentioned advantages of the still loops are equally in force in the timed vectorcardiogram. In addition, virtually every possible

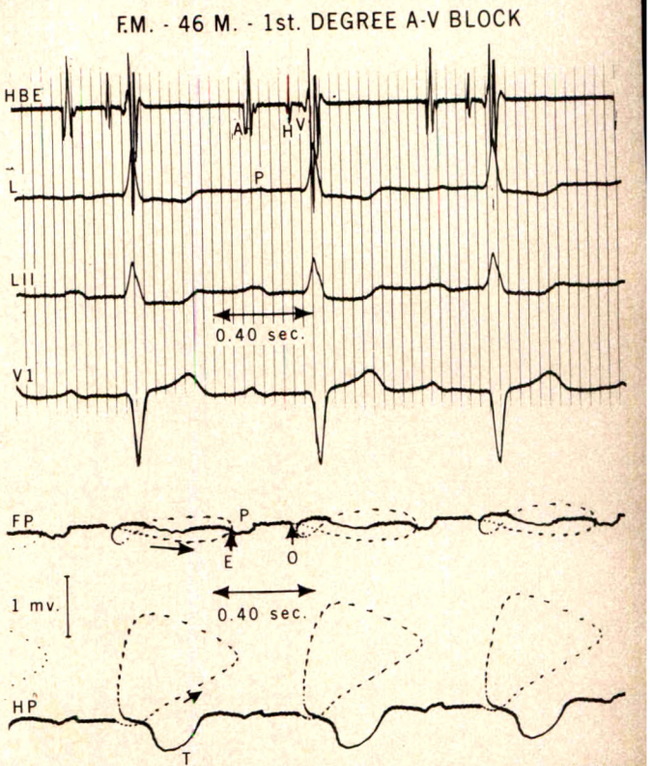

FIGURE 15. Simultaneously recorded His bundle electrogram (HBE), leads I, II and V_1 of the electrocardiogram, with frontal and horizontal plane timed vectorcardiograms in a 46 year old man with idiopathic first degree atrioventricular (A-V) block. The A-H interval is prolonged to 180 msec, thus indicating conduction delay at the level of the A-V node. All surface features of the electrocardiogram relating to A-V and intraventricular conduction are clearly discerned on the biplane vectorcardiogram. A 0.06 second difference between the onset of scalar and vector surface potentials is due to recording in two separate oscilloscopic devices.

combination of bundle branch blocks and variations thereof are easily perceived by recording frontal and horizontal plane running loops simultaneously.[59] Persistence of abnormal frontal plane QRS loop left axis deviation during isolated left anterior fascicular block and intermittent "complete" left bundle branch block suggests that, in the occasional case, QRS loops of posterior orientation and greater than 140 msec duration may be based on various degrees of left bundle bifascicular block.[60] Pathologic identification of fibrotic or degenerative changes in the proximal left bundle branch does not in any way cast discredit on this hypothesis, and definitive examination of the distal fascicular system in such cases will eventually resolve the issue.

Ventricular arrhythmias: Zoneraich and Zoneraich[61] analyzed vectorcardiograms in subjects with bundle branch block patterns arising as a result of ventricular ectopic beats. They recognized distortions of the QRS loops in association with diseases that render the myocardium fibrotic. Interestingly, these investigators[62] have also demonstrated right ventricular pacemaker-induced QRS loop patterns akin to those described for naturally occurring left bundle branch block and myocardial infarction in experimental animals and human subjects. The fact

that these changes were observed in patients with documented acute myocardial infarction lends credence to the proposition that the vectorcardiogram is of practical value for diagnosis when these disturbances occur in combination.

Atrial arrhythmias: High fidelity atrial vectorcardiograms have been recorded in patients with atrial flutter[63] and "left atrial"[64] and "inferior atrial"[65] rhythms. Such studies have been descriptive in nature but, combined with His bundle and intraatrial recordings, may prove useful in the future for delineating the sequence of atrial activation during various rhythm disturbances. Simultaneous recording of the timed vectorcardiogram and His bundle electrogram is feasible in human subjects[58,66] (Fig. 15) and has been applied for evaluation of ventricular depolarization sequences in patients with preexcitation.[67]

Pacemaker Analysis, Single Plane Projection and Computer Application

Gordon[68] presented data that indicated the advantages of pacemaker stimulus artifact analysis using Frank vectorcardiograms. Location, orientation and output of the pacemaker can be established by this technique. Kinoshita and Kobayashi[69] devised a unique method for determining the Y axis deflection in a single horizontal plane QRS loop projection. Representing superior-inferior deflection vectors in the form of colored dashes facilitates the diagnosis of inferior wall infarction by inspection of the horizontal plane QRS loop.

Computer analysis of the vectorcardiogram: Computer analysis has been applied to the diagnosis of numerous cardiac abnormalities, including left ventricular overload[70] and myocardial infarction.[71] During the 1960's some enthusiastic proponents of computer technology suggested that individual analysis of the electrocardiogram and vectorcardiogram would soon be replaced by "rapid-fire" digital printouts. Practical experience over the past decade has not confirmed these speculations. Visual inspection of the P, QRS and T loops is still desirable for definitive interpretation of the vectorcardiogram in the individual case. Superficial and completely qualitative examination of either the XYZ leads or vector loops is to be condemned and has been a pitfall. Careful attention should be directed to the magnitude, duration, rotation and orientation of the critical initial and maximal deflection vectors before diagnostic conclusions are reached. Such analysis permits maximal utilization of information contained in planar loop projections and precludes major individual interpretive variation, which has been documented in the past.[72] Visual inspection or measurement and computer analysis are in no way mutually exclusive, and both techniques in combination are useful for clinical application and research purposes.

In conclusion, our experience, and that of other investigators, has confirmed the practical value of clinical vectorcardiography. It is suggested that this technique be used in all laboratories where the comprehensive noninvasive diagnosis of cardiac disease is undertaken.

Acknowledgment

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Pseudomalfunction of a Beall Mitral Valve Prosthesis in the Presence of Paravalvular Aortic Regurgitation

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Premature closure of a Beall mitral valve prosthesis is described in a patient with aortic prosthetic paravalvular regurgitation. Differentiation from valvular malfunction and diagnostic confirmation by means of cinefluoroscopy and simultaneous electrocardiography are discussed.

As a result of increasing surgical success in valvular heart surgery, the number of patients with prosthetic valves requiring follow-up care is increasing. Evaluation of the function of valve prostheses is complicated by variability in structural characteristics of the prostheses, location of the valves replaced and underlying cardiac function. Detection of malfunction may be quite difficult and requires a thorough knowledge of the auscultatory, echocardiographic and fluoroscopic findings of the prosthesis under evaluation.

This paper describes a patient with both aortic and mitral valve prostheses who had an abnormal prosthetic sound in mid to late diastole. Valve cinefluoroscopy was used to confirm the mitral origin of the sound and to distinguish valve malfunction from early prosthetic closure secondary to paravalvular aortic regurgitation.

Case Report

A 32 year old Negro male alcoholic was admitted to Temple University Hospital on October 2, 1973 with a diagnosis of pneumonia and acute bacterial endocarditis involving both the aortic and mitral valves. The responsible organism in both instances was found to be a type 35 pneumococcus. Despite large dose penicillin therapy, the patient had frank heart failure with an inadequate response to digitalization and diuresis. On November 5, he underwent a limited cardiac catheterization that demonstrated severe mitral and aortic regurgitation with elevation of left ventricular end-diastolic pressure (left ventricle 140/48 mm Hg) and all right heart pressures (right ventricle 80/25, pulmonary arterial wedge 45 mm Hg). These findings and deterioration of the patient's clinical condition prompted emergency valve replacement. At operation, subtotal destruction of both valves and an endocardial abscess of the high ventricular septum were found. The abscess was drained and the valves were replaced with a no. 21 Bjork-Shiley prosthesis in the aortic area and a medium Beall prosthesis in the mitral area.

Postoperatively, the murmurs of aortic and mitral regurgitation were evident. Because of these murmurs, excessive hemolysis and persistent evidence of moderate heart failure, a second cardiac catheterization was undertaken on December 3. At this time, significant paravalvular insufficiency involving both prostheses was identified. Surgical correction was considered but deferred pending improvement in the patient's general condition. On December 13, concern was generated for the patient's continued hemodynamic stability by the appearance of increased intensity of the murmur of aortic regurgitation, a diminished mitral prosthetic closure sound and a mid to late diastolic sound of prosthetic origin. This combination of findings suggested premature closure of the mitral valve prosthesis in association with increasingly severe aortic insufficiency. Prosthetic valve malfunction or detachment, or both, was an additional serious possibility. Valvular cinefluoroscopy was used in an attempt to clarify the diagnosis.

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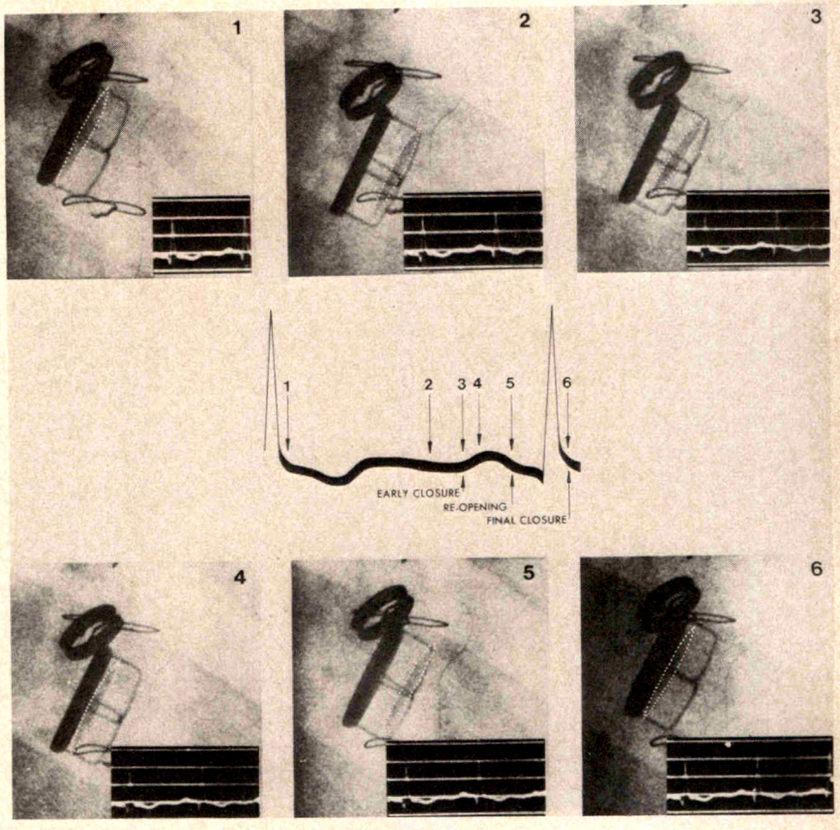

FIGURE 1. Selected sequential frames from the cinefluorogram of a single cardiac cycle with an artist's rendering of the superimposed, simultaneous electrocardiogram. The frames show the valve closed in systole (frame 1) and open in diastole (frame 2), premature closure in later diastole (frames 3 and 4), reopening at the time of atrial contraction (frame 5) and final closure with ventricular systole (frame 6).

Valvular cinefluoroscopy: With use of a Siemens image intensifier with 6-inch magnification mode, the patient was examined in both the right anterior oblique and left anterior oblique positions with the prosthetic base perpendicular to the X-ray beam. Thirty-five millimeter cine films were taken at a rate of 60 frames/sec. An electrocardiogram (lead II) was superimposed on each cine frame (Cinetrace, Electronics for Medicine). Aortic valve motion appeared normal. Although the base of the mitral prosthesis was stable, frame by frame analysis of disc motion and the electrocardiogram revealed that the valve closed prematurely in mid-diastole, reopened with atrial systole and closed again at the time of ventricular contraction (Fig. 1). The simultaneous electrocardiogram demonstrated normal sinus rhythm at a rate of 72/min with a P-R interval of 0.14 second and QRS duration of 0.09 second. It was assumed that premature closure was the result of a significant increase in the amount of paravalvular aortic regurgitation and prompt surgical intervention was undertaken.

At operation, the aortic and mitral paravalvular leaks were oversewn. Postoperatively, mitral prosthetic function returned to normal as determined by auscultation and cinefluoroscopy. The patient was discharged in improved condition 14 days after his second operation.

Discussion

In sinus rhythm, the hemodynamics of closure of a mitral valve prosthesis are similar to those of the normal mitral valve, being influenced directly by the left atrial-left ventricular pressure gradient and mitral valve flow. Closure is initiated shortly after atrial systole and is in part a result of atrial augmentation of left ventricular pressure. Valve closure is then completed by the pressure developed by left ventricular contraction.[1] However, in the presence of prolonged atrioventricular conduction or atrial fibrillation with a long R-R cycle length, the valve may float softly back to partial or complete closure before the onset of ventricular contraction.[1,2] Variation in the intensity or location of the mitral closing sound may represent prosthetic malfunction[3] or indicate a variation in the gradient across the valve orifice secondary to one of several factors including alteration in the rate or character of atrial contraction, underlying ventricular function and pattern of cardiac conduction. In our patient a decrease in the intensity of the mitral closure sound developed with an abnormal sound occurring in mid to late diastole. The association of these findings in a patient with known prosthetic paravalvular aortic regurgitation suggested premature mitral valve closure. This diagnosis was confirmed and prosthetic malfunction excluded using cinefluoroscopy with a simultaneous electrocardiogram imposed on each cine frame. In the selected sequential photographs of valve motion in Figure 1, premature valve closure is clearly visible in frames 3 and 4. Reopening of the valve with atrial contraction and final closure at the time of ventricular contraction is also demonstrated (frames 5 and 6).

Premature closure of mitral valve in severe aortic regurgitation: In sudden severe aortic insufficiency, early closure of the mitral valve has been demonstrated to occur in both experimental animals and clinical situations. Diastolic ventricular pressure is determined by both rate and volume of ventricular

filling, cavity size and wall compliance. In acute severe aortic insufficiency, the ventricular diastolic capacity is exceeded by a combination of forward flow from the left atrium and regurgitant flow across the aortic valve. There is insufficient time for the ventricular cavity to dilate in response to this increased volume load, and further volume results in marked elevation in ventricular pressure. In severe cases, the diastolic pressure exceeds left atrial pressure, resulting in premature closure of the mitral valve.[4,5] Clinical recognition of this entity is of great importance since the prognosis of the patient with severe aortic insufficiency with left ventricular failure is poor without surgical intervention.

Although this phenomenon has not previously been described in a patient with a Beall mitral prosthesis, Agnew and Carlisle[6] described its occurrence in three patients with a Starr-Edwards ball valve prosthesis. In their patients, the valve closed prematurely and did not reopen after atrial systole, a situation more closely representing acute aortic insufficiency with a nondistensible ventricle and high diastolic pressures. In our patient, atrial systole caused reopening of the mitral valve. This finding suggests only moderate elevation of late diastolic pressure, which may represent partial conditioning of the ventricle to larger diastolic volumes or some moderation in the amount of regurgitant flow. It further demonstrates that premature closure with subsequent reopening by atrial systole is a variation in the spectrum of this syndrome and connotes a less serious but still dangerous clinical situation.

Value of cinefluoroscopy of prosthetic valve: We suggest (1) that variation in the intensity or location of the mitral prosthetic closing sound be investigated by use of cinefluoroscopy, and (2) that the patient with a prosthetic valve undergo valve cinefluoroscopy early after operation and at yearly intervals thereafter. Comparison of these serial observations with cinefluoroscopic findings at the time of suspected prosthetic malfunction will facilitate differentiation of normal from abnormal valve motion. Further help in determining the timing of valve motion may be necessary and, as in our case, a superimposed frame by frame simultaneous electrocardiogram may be useful.

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Limitations of the Surface Electrocardiogram in Diagnosis of Atrial Arrhythmias

Further Observations on Dissimilar Atrial Rhythms

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Electrophysiologic studies with recordings of multiple intracavitary electrograms were performed in two patients with atrial dysrhythmias. In Case 1 the arrhythmic pattern in the surface electrocardiogram resembled atrial flutter. Electrophysiologic studies revealed the arrhythmia to be paroxysmal left atrial tachycardia, with separation of left and right atrial components of the P wave by an isolectric period secondary to marked interatrial conduction delay. In Case 2 the surface electrocardiogram indicated paroxysmal atrial tachycardia with block. Electrophysiologic studies revealed right atrial standstill with atrial inexcitability and two dissimilar rhythms involving the left atrium. The electrocardiograms did not accurately reflect atrial arrhythmias in these two patients and only multiple direct recordings permitted the correct diagnoses. New electrophysiologic observations concerning intraatrial block and dissimilar atrial rhythms are presented.

Atrial dysrhythmias are usually easily recognizable in the surface electrocardiogram with the type and timing of P waves reflecting underlying atrial activity. However, in some patients, direct recording techniques are necessary for accurate and complete diagnosis. Zipes and DeJoseph[1] recently reported on several patients with dissimilar atrial rhythms that required direct recording techniques for diagnosis. In this study, we present further observations concerning the limitations of surface electrocardiography in patients with atrial dysrhythmias. In one of our patients, the electrocardiographic pattern resembled atrial flutter, whereas electrophysiologic studies revealed the arrhythmia to be paroxysmal atrial tachycardia with marked left to right interatrial block. In the second patient electrocardiograms suggested paroxysmal atrial tachycardia, whereas direct studies revealed multiple (three) dissimilar atrial rhythms.

Methods

Electrophysiologic studies were performed in two patients with atrial dysrhythmias. Informed consent was obtained before the studies. Two electrode catheters (one bipolar and one quadripolar) were percutaneously passed to the right heart chambers and utilized for one or more of the following: (1) recording of right atrial electrograms from multiple sites, (2) right atrial stimulation, (3) recording of coronary sinus (left atrial) electrograms, and (4) recording of His bundle electrograms. A bipolar electrode catheter was also passed to the esophagus and used to record left atrial electrograms.

Standard leads I, II, III and V_1 and multiple atrial electrograms were recorded simultaneously on a multichannel oscillosopic recorder (Electronics for Medicine DR-16) at paper speeds of 100 and 200 mm/sec. Electrical stimuli were provided by a digital programmable pulse generator (constructed by

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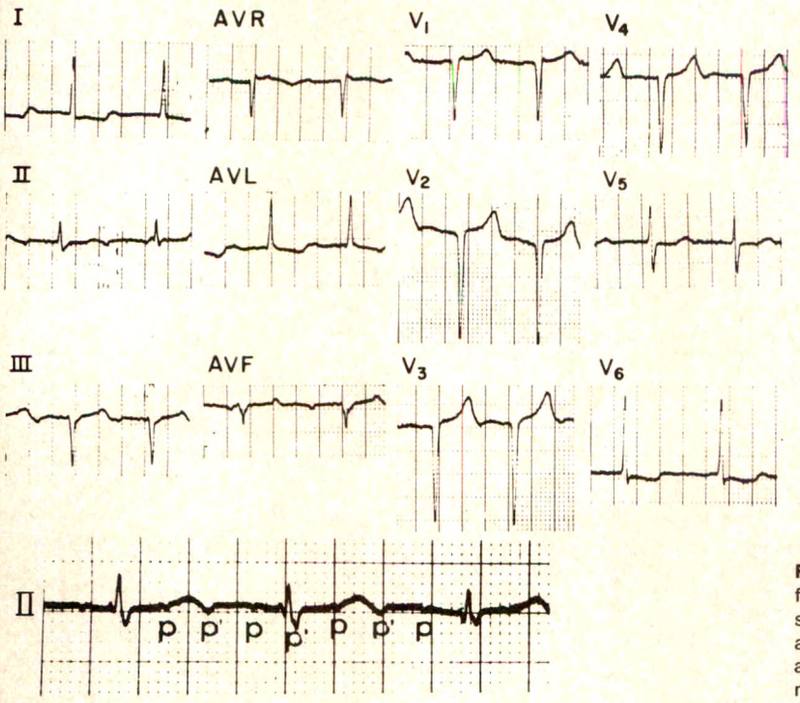

FIGURE 1. Case 1. Electrocardiograms reveal "atrial flutter" (rate 340/min), with irregular ventricular response and nonspecific ST-T wave changes. There is alternation of smaller (P) and larger (P′) waves, which are both inverted in leads II, III and aVF. An enlargement of the rhythm strip is shown at bottom.

M. Bloom, Philadelphia, Pa.). Refractory periods were measured with the extrastimulus technique.[2,3] The test stimulus (S_2) was introduced after every eighth driven stimulus (S_1). The S_1-S_2 interval was decreased in 10 msec increments. Conduction intervals and refractory periods were defined and measured as previously described.[2,3]

Results

Case 1

This was a 68 year old man with chronic obstructive lung disease with cor pulmonale and thyroglossal tumor. He was not taking cardiac medications. Electrocardiograms were interpreted as revealing atrial flutter (rate 340/min), with varying atrioventricular (A-V) block and nonspecific ST-T wave changes. Close inspection of the electrocardiogram (Fig. 1) revealed alternation of atrial activity between smaller and larger atrial complexes both of which were inverted in leads II, III and aVF.

Electrophysiologic studies with simultaneous recording of multiple surface leads, left atrial electrograms (from the esophagus) and right atrial electrograms revealed the rhythm to be atrial tachycardia at half the rate of the previously interpreted flutter rate (162/min) (Fig. 2A). Activation of the atria appeared to be from left to right, the interval between left (A_L) and right atrial (A_R) electrograms being 165 msec. The smaller atrial complexes (P_L) in the surface electrocardiogram coincided with the onset of the left atrial electrogram, whereas the larger surface atrial complex (P_R) coincided with the onset of the right atrial electrogram (Fig. 2A). Thus, the apparently alternating flutter waves in the surface electrogram reflected the left and right atrial components of a single P wave with a duration of 220 msec, secondary to marked interatrial block. His bundle recordings revealed varying A-V block with the site of block proximal to the His bundle.

The atrial tachycardia was transiently converted to normal sinus rhythm after sudden cessation of rapid high right atrial pacing at a rate of 428/min (cycle length 140 msec) (Fig. 2B). P waves after conversion revealed an atrial activation sequence of right to left, with a duration of 205 msec. The interval between the right and left atrial electrograms (A_R-A_L) was 150 msec. Normal sinus rhythm lasted for only several beats and was followed by immediate resumption of the left atrial tachycardia.

Atrial extrastimuli were introduced at a driving cycle length of 310 msec, which constantly captured the atria (Fig. 3). Conduction time between the right and left atria (A_R-A_L interval) increased progressively as coupling intervals were decreased (Fig. 3, A and B). Left atrial tachycardia resumed immediately after each capturing extrastimulus with a returning interval of 240 msec, thereby suggesting that an ectopic focus was discharged and reset by the premature atrial stimulation. The atrial functional and effective refractory periods were 150 and 140 msec, respectively (Fig. 3, B and C). Although these periods seem short, there are no comparable normal data in man for the driven cycle length of 310 msec.

Comments: Our findings suggest that paroxysmal atrial tachycardia with marked interatrial block can mimic atrial flutter in the surface electrocardiogram. Direct recording techniques were necessary for proper delineation of the rhythmic disturbance. This tachycardia in our patient appeared to be ectopic rather than reentrant since single extrastimuli appeared to reset it. In this patient there was also a marked discrepancy between interatrial conduction time, which was long, and atrial refractory periods, which were short.

Case 2

This was a 64 year old man, admitted to the University of Illinois Hospital because of dyspnea and leg edema. For the past 2 years, he had been taking digoxin (0.25 mg/day)

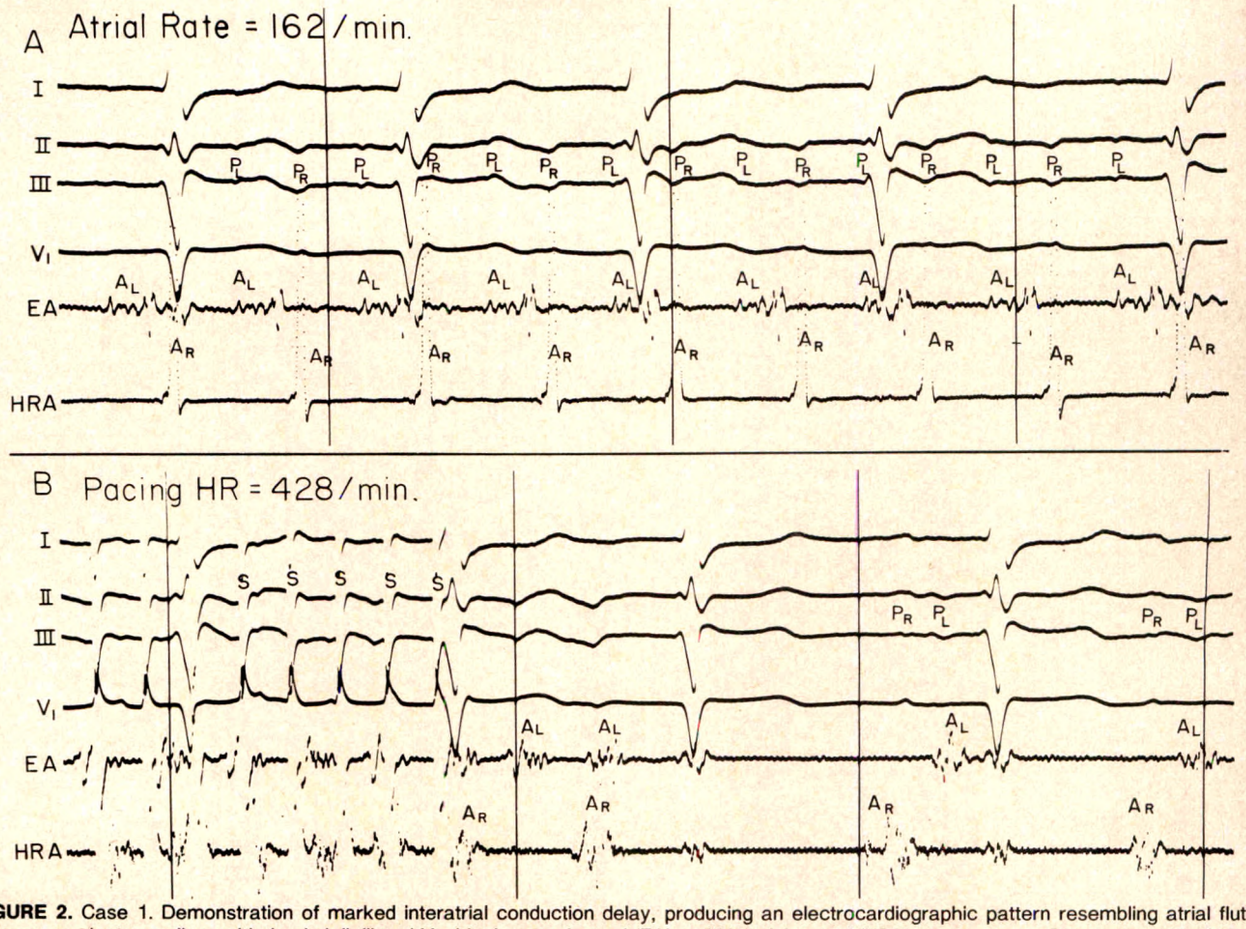

FIGURE 2. Case 1. Demonstration of marked interatrial conduction delay, producing an electrocardiographic pattern resembling atrial flutter. Shown are electrocardiographic leads I, II, III and V_1, bipolar esophageal (EA) and high right atrial (HRA) electrograms. Paper speed is 100 mm/sec, and time lines are at 1-second intervals in this and subsequent illustrations. **Panel A** discloses paroxysmal left atrial tachycardia (rate 162/min), with left (A_L) to right (A_R) atrial activation sequence. Note that the smaller and the larger P waves (P_L and P_R) in the surface electrocardiograms coincided with the onset of the left (A_L) and right (A_R) atrial electrograms, respectively. **Panel B** reveals conversion of tachycardia to sinus rhythm with rapid atrial stimulation (S) at a rate of 428/min. The two beats on the right are sinus. Note the change in P wave configuration and atrial activation sequence after conversion. HR = heart rate.

and diuretic agents for congestive heart failure. Chest X-ray examination revealed marked cardiomegaly with enlargement of all four chambers.

Electrocardiograms revealed atrial tachycardia (170/min) with varying block and periods of A-V dissociation, and complete left bundle branch block (QRS interval = 0.12 second) (Fig. 4). The P waves were inverted and seen clearly only in lead V_1. Values for serum electrolytes, creatinine and enzymes (glutamic oxaloacetic transaminase [SGOT], lactic dehydrogenase [LDH] and creatine phosphokinase [CPK]) were normal. Despite discontinuance of digoxin, paroxysmal atrial tachycardia with block persisted.

Electrophysiologic studies were performed 1 week after admission. Surface lead V_1 revealed the previously noted atrial tachycardia with an atrial rate of 162/min (cycle length 365 msec) (Fig. 5). Intraatrial recordings from the high, mid and low lateral right atrium revealed absence of atrial activity (atrial standstill) despite maximal signal amplification (Fig. 5). Recording of left atrial electrograms from the coronary sinus revealed a left atrial tachycardia, with irregular irregularity. The cycle lengths of left atrial complexes ranged from 220 to 380 msec (Fig. 5). These coronary sinus atrial electrograms bore no apparent relation either to P waves in the surface electrocardiogram or to QRS complexes. His bundle electrograms revealed sporadic, very low amplitude, atrial potentials with His bundle potentials preceding each QRS complex (H-V intervals 100 msec). R-R intervals ranged from 585 to 775 msec with a mean heart rate of 90/min. Atrial pacing was attempted from multiple right atrial sites. The atria were totally inexcitable, despite a maximal stimulus amplitude of 22 milliamperes.

On the day after electrophysiologic study, a bipolar electrode catheter passed to the esophagus revealed a regular atrial rhythm, with a rate of 324/min (cycle length 182 msec) (Fig. 6). This rhythm had a 2:1 relation to the atrial tachycardia recorded in the surface electrocardiogram.

Comment: In this patient, surface electrocardiograms revealed chronic paroxysmal atrial tachycardia with varying block. Direct recording techniques from both the right and left atria revealed no electrogram with a 1:1 correspondence to this rhythm. However, direct recording techniques revealed the following additional multiple dissimilar atrial rhythms: (1)

right atrial standstill with atrial inexcitability; (2) left atrial tachycardia with irregular irregularity, recorded from the coronary sinus; and (3) left atrial flutter with twice the rate of the surface paroxysmal atrial tachycardia, recorded from an esophageal lead 1 day after the initial electrophysiologic study. Presumably, paroxysmal atrial tachycardia recorded in the surface electrogram reflected 2:1 intraatrial block of this flutter. The portion of the atria responsible for the surface paroxysmal atrial tachycardia could not be determined.

It is not known whether the coronary sinus and esophageal electrodes sampled similar portions of the left atrium, and since the two left atrial rhythms were recorded on different days, it is uncertain whether there were two simultaneous dissimilar rhythms involving the left atrium or two different left atrial rhythms on different days. Because of the 2:1 relation of the flutter and the paroxysmal atrial tachycardia, and because the paroxysmal atrial tachycardia persisted at the same rate on both days, it is likely that the arrhythmia recorded with the esophageal lead was present although not recorded during the initial electrophysiologic study.

In summary, this patient had at least three and possibly four simultaneous dissimilar atrial rhythms.

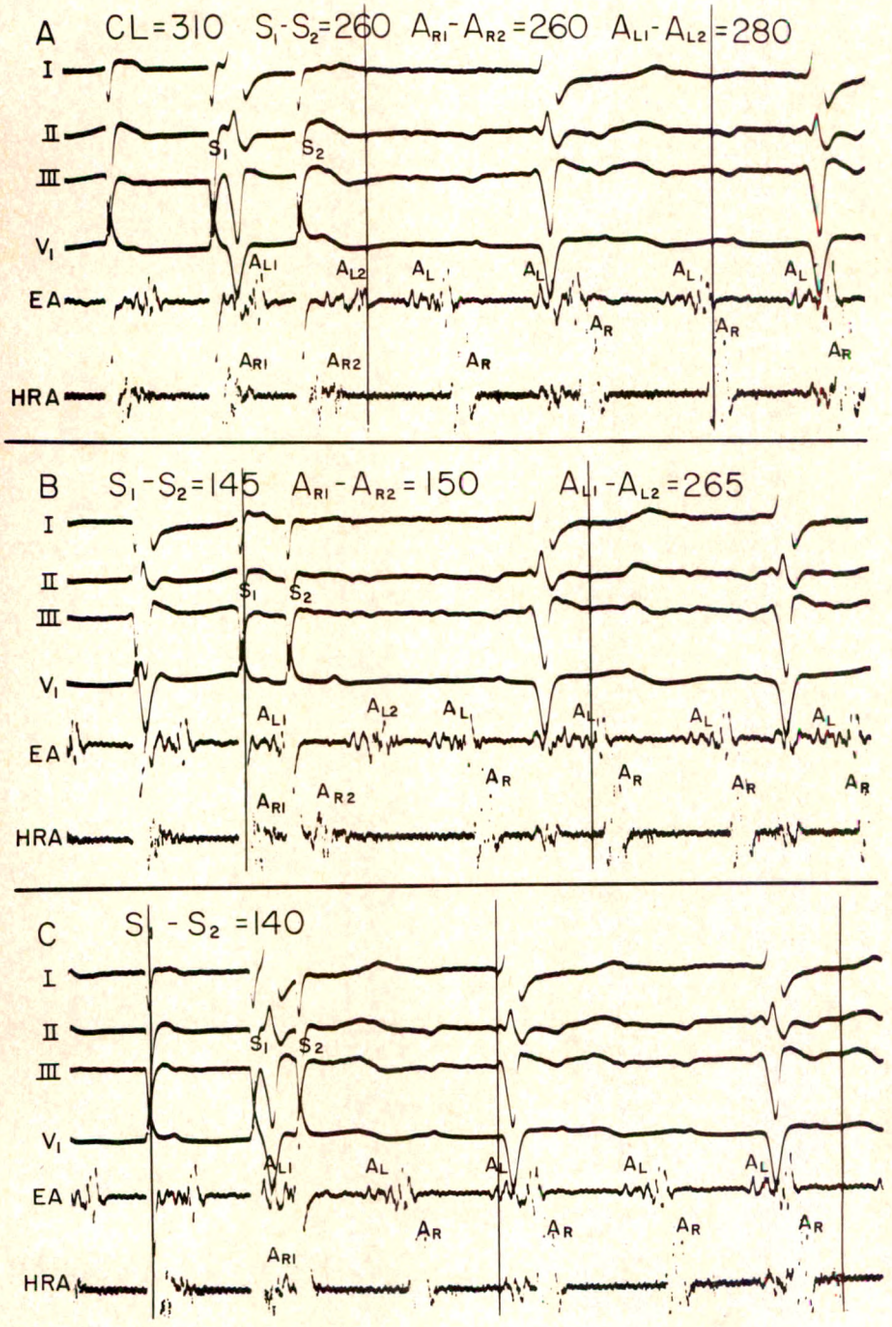

FIGURE 3. Case 1. Recording disclosing refractory periods of the atrium. S_1, A_{L1}, and A_{R1} indicate, respectively, stimulus artifact and left and right atrial electrograms of the driven beats; S_2, A_{L2} and A_{R2} indicate, respectively, stimulus artifact and left and right atrial electrograms of the test beats. The driving cycle length (CL) was 310 msec. In **Panel A,** S_1-S_2 and A_{R1}-A_{R2} were both 260 msec; A_{L1}-A_{L2} was 280 msec and A_{L2}-A_L 240 msec. In **Panel B,** S_1-S_2 was 145 msec, A_{R1}-A_{R2} was 150 msec and A_{L1}-A_{L2} lengthened to 265 msec because of increased interatrial conduction delay. The atrial functional refractory period was 150 msec. A_{L2}-A_L was again 240 msec. In **Panel C,** an atrial effective refractory period of 140 msec was achieved. Note the resumption of paroxysmal tachycardia immediately after the extrastimulus.

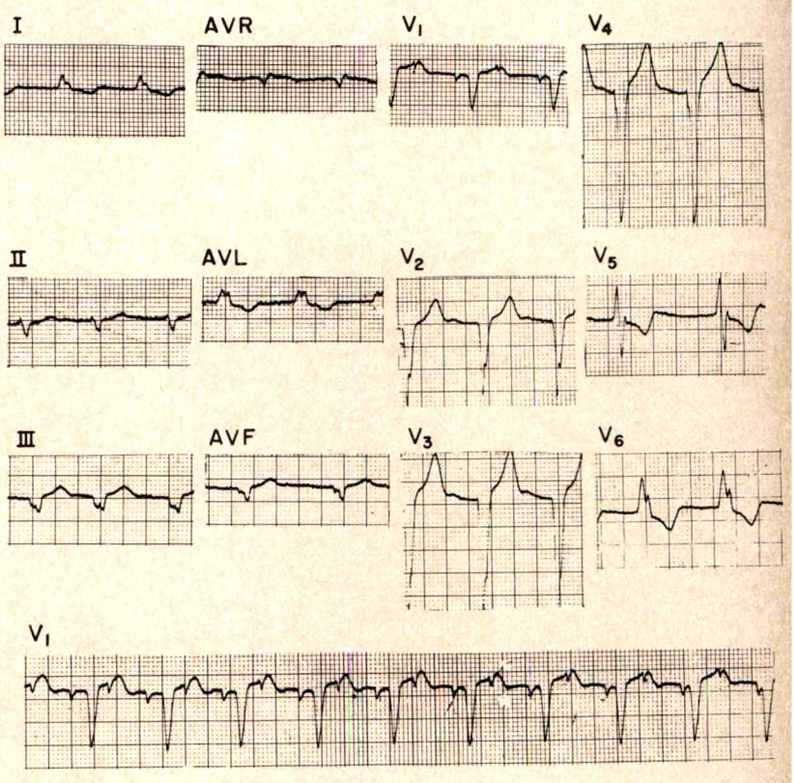

FIGURE 4. Case 2. Electrocardiogram discloses paroxysmal atrial tachycardia (rate 170/min) and varying A-V block with periods of junctional tachycardia and complete left bundle branch block.

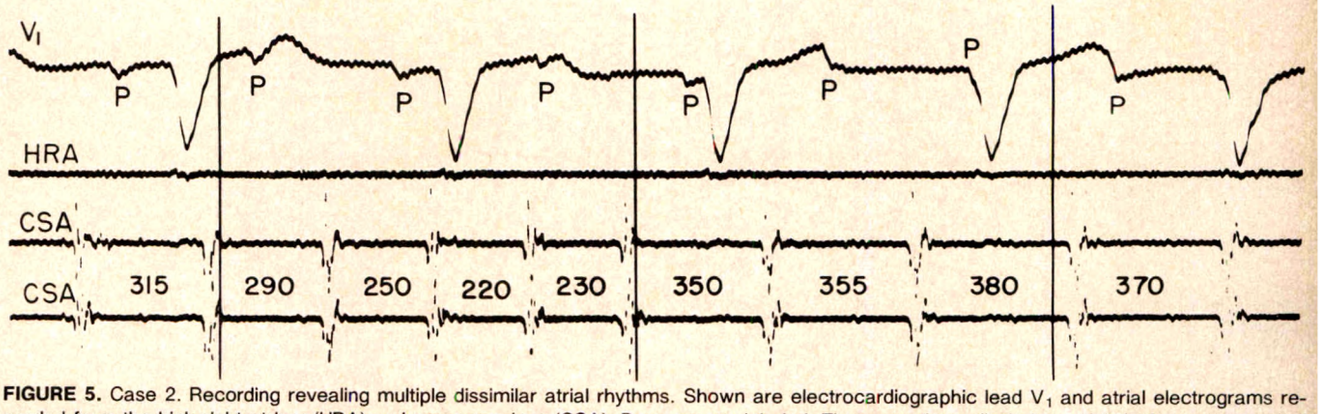

FIGURE 5. Case 2. Recording revealing multiple dissimilar atrial rhythms. Shown are electrocardiographic lead V_1 and atrial electrograms recorded from the high right atrium (HRA) and coronary sinus (CSA). P waves are labeled. There are three dissimilar atrial rhythms: paroxysmal atrial tachycardia (V_1), right atrial standstill (HRA) and a rapid irregular left atrial rhythm of varying cycle lengths (220 to 380 msec) (CSA).

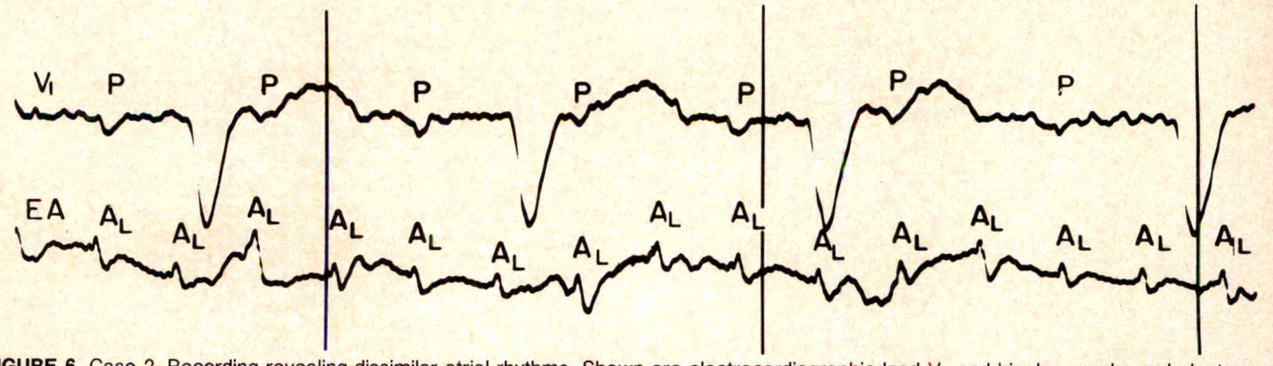

FIGURE 6. Case 2. Recording revealing dissimilar atrial rhythms. Shown are electrocardiographic lead V_1 and bipolar esophageal electrogram (EA). Lead V_1 shows paroxysmal atrial tachycardia, whereas the esophageal electrogram shows atrial flutter. The atrial electrogram (A_L) has a 2:1 relation to the P waves in lead V_1.

It was impossible to determine which atrial rhythm controlled the ventricles.

Discussion

The mode of impulse transmission between the sinus node, atria and A-V node is still a matter of debate. Sir Thomas Lewis,[4] in studies of the canine heart, suggested that the electrical impulse in the normal heart originates in the sinus node and spreads through both atria in a radial or syncytial wave form to reach the A-V node. Studies by Spach et al.[5] and others[6,7] support this view. On the other hand, many workers[8-14] have suggested the existence of specialized or preferential pathways in the atria. James[15] and other investigators[16–26] have provided anatomic and electrophysiologic evidence supporting the existence of preferential atrial conduction. Their studies demonstrated three internodal tracts (anterior, middle and posterior) connecting the sinus and A-V nodes. In addition, an extending branch to the left atrium (Bachmann's bundle) arising from the anterior internodal tract was also demonstrated.

Intraatrial and Interatrial Block

Intraatrial or interatrial block is characterized by abnormally wide P waves during sinus rhythm or by changes in P wave configuration during sinus rhythm or after a premature beat.[18,27,28] James and Sherf[18] suggested that the blocks occur in the internodal tracts. Recent experiments in canine hearts by Waldo et al.[26] demonstrated that P wave duration increased significantly whereas P wave configuration and polarity remained unchanged after the anterior internodal tract was cut close to the sinus node. A lesion placed in the Bachmann's bundle adjacent to the interatrial septum produced significant changes in P wave polarity, configuration and duration resembling "P mitrale." These studies suggested that the specialized atrial tracts were functionally significant in activation of the atria.

The diagnosis of intraatrial or interatrial blocks can be facilitated by direct intracavitary recordings. In Case 1, with severe interatrial block, several interesting electrophysiologic phenomena were seen. First, the degree of interatrial delay was such that the two components (left and right atrial) of the P wave were separated by an isoelectric period, producing an electrocardiographic pattern resembling atrial flutter. Second, the interatrial delay prolonged the P wave duration to 220 msec. Third, despite severe interatrial delay, the atrial functional refractory period was only 150 msec. This short atrial functional refractory period almost certainly reflected the short driving cycle length, since atrial functional refractory period decreases as cycle length shortens.[3] Although refractory periods were not measured at multiple sites, this result also suggests a major discordance between intraatrial conduction time and refractory period in this patient. A similar discordance between long conduction time and short refractory period in the diseased His-Purkinje system was recently described by Wu et al.[29] Finally, Case 1 is another instance of direct demonstration of left atrial rhythm by intracavitary recordings.[30]

Atrial Dissociation

Atrial dissociation of the right and left atria, with two independent P waves, has been reported in both human and animal hearts.[31–35] This occurrence has usually been attributed to complete intraatrial or interatrial block. The basic rhythm is usually sinus, but may be an ectopic atrial rhythm, junctional rhythm or even atrial fibrillation or flutter. The dissociated rhythm may be a slow escape rhythm, atrial tachycardia or fibrillation or flutter, and it is not conducted to the ventricles. The atrial complexes of the ectopic dissociated rhythm are usually smaller than those of the basic rhythm, probably because a smaller portion of the atrium is depolarized. Despite electrocardiographic observations, the true existence of this phenomenon was questionable, since direct intracavitary recordings were rarely performed. Recently, Zipes and DeJoseph,[1] using multiple intracavitary recordings, demonstrated dissimilar atrial rhythms with fibrillation in one atrium and a slower, more regular activity in the other. Their results suggested that the slower, more regular rhythm in one atrium was a result of constant filtering of the fibrillatory waves coming from the other atrium, due to a fairly fixed refractory period in the latter.

In our Case 2, with multiple dissimilar atrial rhythms, the electrophysiologic findings could be explained by postulating right atrial standstill and multiple ectopic foci in the left atrium. For this to occur, protective entrance and exit block in various ectopic foci must also have been present, since multiple foci would interfere with each other if there were no block. An alternative and more plausible explanation, as suggested by Zipes and DeJoseph,[1] was right atrial standstill and a rapid firing focus in the left atrium. Diverse refractory periods of atrial muscles in various sites of the atrium resulted in multiple atrial rhythms. Right atrial standstill presumably reflected advanced right atrial disease.

Both of our cases suggest that, under unusual circumstances, the surface electrocardiogram may not accurately portray atrial activation, particularly in the presence of advanced atrial disease. Manifestation of atrial rhythms at various recording sites including the surface electrocardiogram is dependent on the mass of atrial depolarization and proximity of the recording electrodes to the atrial mass.

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"Paradoxical" Prolongation of Sinus Nodal Recovery Time After Atropine in the Sick Sinus Syndrome

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A case of symptomatic sick sinus syndrome is presented with confirmation of sinus nodal dysfunction established by functional testing. The validity of such provocative testing and the criteria for abnormality are discussed. A newly recognized, seemingly "paradoxical" and potentially detrimental effect of atropine noted in this patient is examined. Despite an increase in sinus rate and an improvement in sinoatrial conduction time after administration of atropine, a markedly prolonged sinus recovery time after rapid atrial pacing occurred, and atrial quiescence for more than 10 seconds was seen. Possible electrophysiologic mechanisms for this phenomenon, such as decreased atriosinus entrance block, concealed sinoatrial reentry or enhanced intranodal depolarization, are discussed and potential clinical correlates are made.

The "sick sinus syndrome" has been recognized with increasing frequency since 1968 when Ferrer[1] called attention to a group of related disorders whose signs and symptoms stem from sinus nodal dysfunction. The various clinical manifestations of these disorders have been well described.[1–7] and methods of documenting or quantitating the functional defects are improving. Ambulatory monitoring, one useful means of documenting such defects, allows observation of the electrocardiographic pattern during symptomatic periods. Pharmacologic interventions and provocative testing with atrial stimulation are additional useful tools for demonstrating otherwise latent or intermittent dysfunction. These advances in diagnostic technology have resulted in increased recognition of sinus nodal dysfunction and consequently in more frequent attempts at therapy, generally with permanent pacemaker implantation.[2,4] Pharmacologic therapy such as vagal blockade is employed less frequently and has often been unsuccessful. It may also be potentially detrimental. We recently studied a patient with the sick sinus syndrome in whom administration of atropine "paradoxically" lengthened the sinus nodal recovery time after atrial pacing. This occurred despite an increase in sinus rate and improvement in sinoatrial conduction after administration of the drug. The results of functional testing and our explanation for the response of the sinus recovery time to atropine form the basis of this report.

Case Report

A 55 year old woman was referred for functional testing of the sinus node. She had no cardiovascular symptoms until the onset of increasingly frequent "skipped beats" 4 years before admission. At that time sinus bradycardia was first noted. One year before admission, she first experienced exertional dyspnea and light-headedness that became progressively more severe. At no time did she experience true syncope, angina, congestive heart failure or rapid palpitations.

On hospital admission, blood pressure was 100/70 mm Hg and pulse 53 beats/min with occasional pauses; respirations were 16/min and temperature was normal. Cardiac examination revealed normal size and thrust, normal sounds, a functional systolic ejection murmur but no gallop or rub. Routine laboratory data were unremarkable except for the electrocardiogram, which

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disclosed a mean sinus rate of 48 beats/min. A Valsalva maneuver caused the pulse rate to decrease to 40 beats/min where it remained until glottal release. Twenty-four hour dynamic electrocardiography revealed sinus bradycardia, moderately frequent supraventricular premature beats, repeated episodes of sinoatrial Wenckebach phenomena, as well as 3 to 5 second periods of asystole. Electrophysiologic studies were then performed to quantitate the severity of sinoatrial dysfunction and to assess the response to vagolytic drugs.

Electrophysiologic Methods

The patient was studied in the cardiac catheterization laboratory in the resting, nonsedated postabsorptive state. Under fluoroscopic monitoring a no. 6F tripolar catheter used to record the His bundle electrogram was passed percutaneously by way of the right femoral vein to the right atrium to lie across the tricuspid valve, and a no. 6F quadripolar catheter, one pair of electrodes for stimulating and one pair for recording, was passed through a right antecubital vein into the right atrium. The stimulating electrodes were positioned along the lateral wall of the mid-right atrium and the recording electrodes at the junction of the superior vena cava and the right atrium. Signals from the atrial and His bundle electrodes and the body surface electrocardiogram were displayed simultaneously on an Electronics for Medicine multichannel oscillograph and recorded on frequency-modulated magnetic tape. Control recordings of spontaneous rhythm were obtained before the initiation of atrial stimulation. Premature atrial stimuli were introduced by means of the stimulating electrodes during spontaneous sinus rhythm. The atrial electrogram was used to initiate a programmable Ortec stimulator. In this way, atrial premature stimuli of twice diastolic threshold intensity and 2 msec in duration were introduced by means of an isolation transformer after every eighth spontaneous sinus cycle and moved in 20 msec increments. The entire atrial diastolic period was scanned twice. Rapid atrial pacing at cycle lengths of 1,000, 900, 800, 700, 600, 500 and 400 msec was performed four times at each atrial cycle length with use of the same electrode pair. By means of the Electronics for Medicine recorder, the data were transferred to photographic paper for analysis at a paper speed of 100 mm/sec.

When rapid pacing was performed, the following were measured: (1) the interval from the last driven atrial depolarization to the next spontaneous depolarization of any type, and (2) the interval from the last driven atrial depolarization to the next spontaneous P wave if this interval was different from the first. Sinus recovery time was defined as the interval from the last driven atrial depolarization during rapid atrial pacing to the next spontaneous P wave if it was of sinus origin.

When the spontaneous sinus cycle was interrupted by an atrial premature depolarization, the following were measured: (1) the interval between the last two spontaneous P waves preceding the atrial premature depolarization, that is, the spontaneous sinus cycle length (A_1-A_1); (2) the interval between the last spontaneous sinus P wave and the atrial premature depolarization, that is, the test cycle (A_1-A_2); (3) the interval between the atrial premature depolarization and the following spontaneous P wave, that is, the return cycle (A_2-A_3); and (4) the spontaneous sinus cycle immediately following the return cycle, that is, the postreturn cycle (A_3-A_4).

Rapid atrial pacing and atrial premature stimulation were subsequently repeated 5 minutes after the administration of 1 mg of atropine intravenously when the pulse rate stabilized at a new level.

Results

The electrophysiologic data obtained at the time of catheterization were as follows:

Control Studies

Rhythm and rate: Sinus arrhythmia with atrial cycle lengths ranging from 1,025 to 2,507 msec was the predominant rhythm throughout the 60 minute testing period. Brief periods of junctional escape beats were noted, some with retrograde atrial depolarization (Fig. 1). The mean sinus cycle length (1,200 beats) was 1,479 msec.

Rapid atrial pacing: The values for sinus recovery time were generally similar at a given frequency of stimulation, and all postpacing pauses were terminated by sinus impulses (Fig. 2). In three of the four trials, the value of sinus recovery time rose to a peak at a pacing interval of 700 msec, with a maximum of 2,632 msec, and then decreased progressively. When the driven atrial cycle length was 400 msec in these three trials, the mean sinus recovery time was 1,543 msec (Fig. 2, point A, and Fig. 3A). However, in the fourth trial, the sinus recovery time at a paced cycle length of 400 msec was 3,325 msec, thus suggesting that 2:1 sinoatrial exit block had occurred (Fig. 2, point B, and Fig. 3B).

Premature atrial stimulation: An estimated mean sinoatrial conduction time was calculated from the plot of A_2-A_3 versus A_1-A_2 (Fig. 4A) using previously published principles.[13] The vertical line seen in this display represents an A_1-A_2 interval equal to the mean of all spontaneous atrial cycle lengths in sinus rhythm whereas the lower horizontal line represents an A_2-A_3 interval also equal to the mean spontaneous atrial cycle length. The upper horizontal line represents an A_2-A_3 interval equal to two spontaneous atrial cycle lengths. Points falling on the middle diagonal line represent nonreset of the sinus nodal pacemaker by the atrial premature depolarization (A_2). These late diastolic premature depolarizations do not have time to penetrate and reset the sinus node before it fires spontaneously and thus are followed by a fully compensatory pause. For these points, A_1-A_2 plus A_2-A_3 = $2(\overline{A_1\text{-}A_1})$. Atrial premature depolarizations elicited earlier in atrial diastole yield A_2-A_3 intervals that fall below and to the left of the middle diagonal line as sinus pacemaker reset occurs; that is, when the premature depolarization penetrates and depolarizes the sinus node before its next expected spontaneous firing, the sinus pacemaker is reset. The return cycle is no longer fully compensatory but is greater than one spontaneous sinus cycle length.

The value of A_2-A_3 represents the duration of conduction from the induced atrial premature depolarization into the sinus node, at which point reset occurs, plus the time until the next spontaneous sinus depolarization occurs (presumed equal to $\overline{A_1\text{-}A_1}$) plus the duration of conduction out of the sinus node to the atrium, when the next atrial depolarization occurs. Thus, A_2-A_3 equals $\overline{A_1\text{-}A_1}$ plus conduction time

into and out of the sinus node. Therefore, A_2-A_3 minus A_1-A_1 (which is represented by the distance of these points above the lower horizontal line) equals twice the sinoatrial conduction time. The mean of all A_2-A_3 intervals in this zone was determined and a mean sinoatrial conduction time was calculated from the formula $[(\overline{A_2\text{-}A_3}) - (\overline{A_1\text{-}A_1})]/2$.

Despite the borderline normal value of 83 msec so obtained, several return cycles were compatible with 2:1 sinoatrial exit block. These points, not used in calculating the mean sinoatrial conduction time, are also seen in Figure 4A. When 2:1 sinoatrial exit block occurs, A_3 is delayed by a time equal to one sinus cycle length; that is, the curve shifts upward a dis-

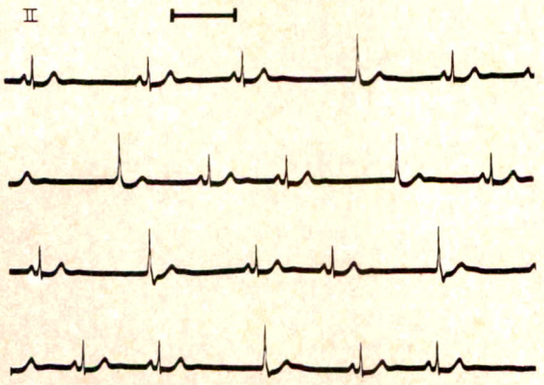

FIGURE 1 (above). Lead II rhythm strip at the onset of electrophysiologic testing revealing sinus rhythm with junctional escape beats. Time bar equals 1 second.

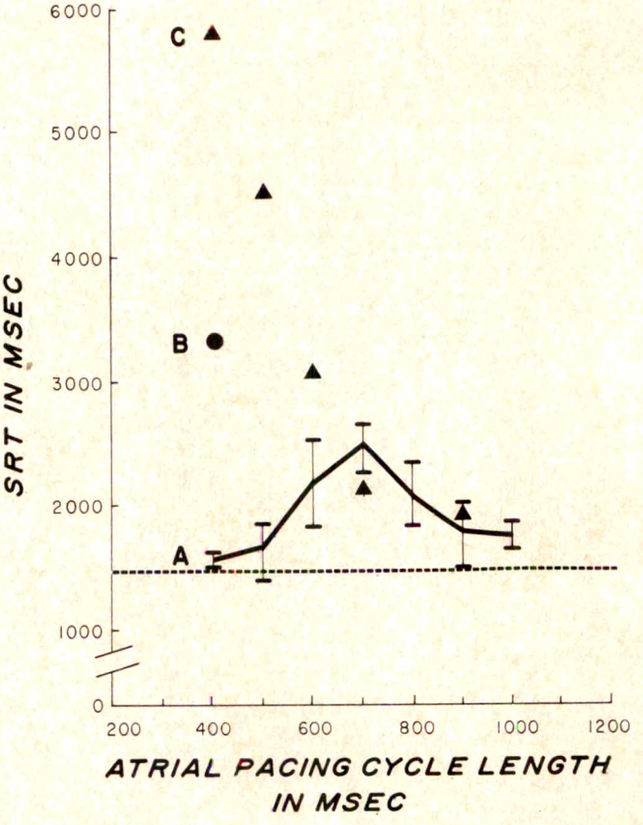

FIGURE 2 (right). Rapid atrial pacing. Postpacing pauses (sinus recovery times, SRT) are plotted against driven atrial cycle length. Bars represent range of pauses at each pacing frequency in control state (see text). **Continuous line** connects mean values. **Triangles** indicate pauses at corresponding pacing frequencies after administration of atropine. **Point A** = mean sinus recovery time at a driven atrial cycle length of 400 msec for three of four trials in the control state. **Point B** = pause representing probable 2:1 sinoatrial exit block in the fourth trial at a driven atrial cycle length of 400 msec in the control state. **Point C** = junctional escape beat without retrograde conduction to the atria at a driven atrial cycle length of 400 msec after administration of atropine. **Dashed horizontal** line represents mean sinus cycle length.

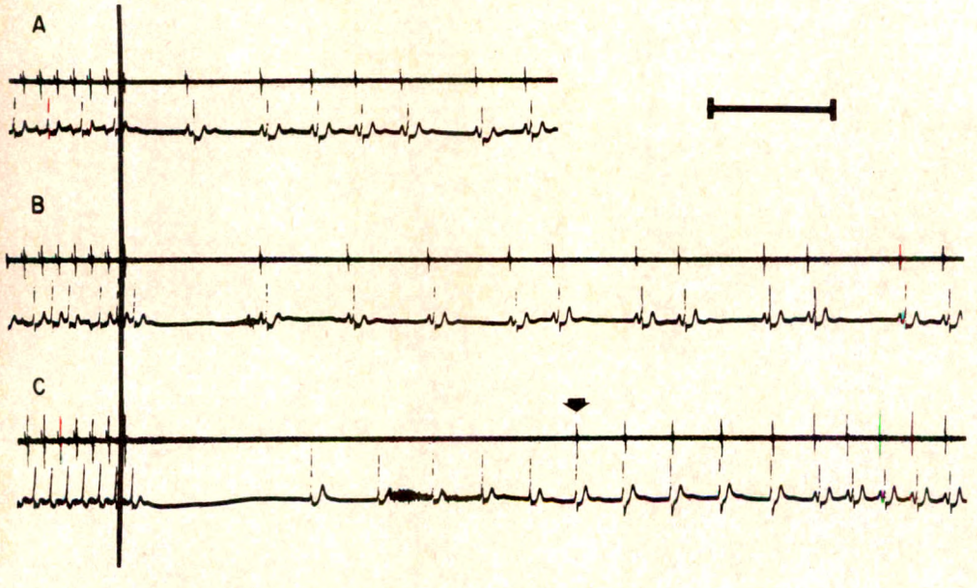

FIGURE 3. Termination of atrial pacing at driven atrial cycle lengths of 400 msec. **Panel A,** indicating results in three of four trials in the control state, corresponds to point A in Figure 2. **Panel B,** indicating 2:1 sinoatrial exit block in the fourth trial in the control state, corresponds to point B in Figure 2. **Panel C,** indicating results after administration of atropine, corresponds to point C in Figure 2. Note the absence of atrial activity for 10,920 msec. **Arrow** indicates earliest atrial complex after pacing. The first five P waves to return result from atrial activation from junctional escape beats. Sinus P waves follow. Time bar equals 3 seconds.

tance equal to A_1-A_1. Points then fall on the upper diagonal line or below and to the left of it, depending on the prematurity of the atrial premature depolarization. The lower diagonal line in this figure indicates where return cycles following interpolated atrial premature beats would have occurred. The mean post-return cycle (A_3-A_4), not shown on this plot, was not significantly different from the mean of all other sinus cycles.

Atrioventricular conduction: A-H and H-V intervals were normal, however, A-H Wenckebach phenomenon appeared with a paced atrial cycle length of 500 msec.

After Atropine

Rhythm and rate: The mean atrial cycle length shortened to 953 msec in the steady state after administration of atropine.

Rapid atrial pacing: On all but one occasion the postpacing pauses were lengthened by comparison with the mean value of sinus recovery time at equivalent pacing rates before administration of atropine

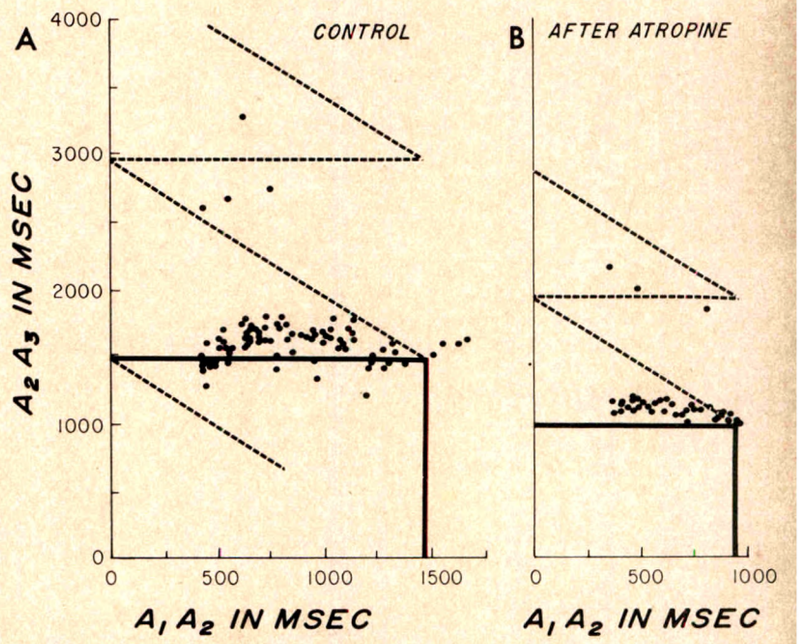

FIGURE 4. The return cycle (A_2-A_3) plotted as a function of the test cycle (A_1-A_2) during atrial premature stimulation. **Panel A** = control state; **Panel B** = state after administration of atropine. See text for details.

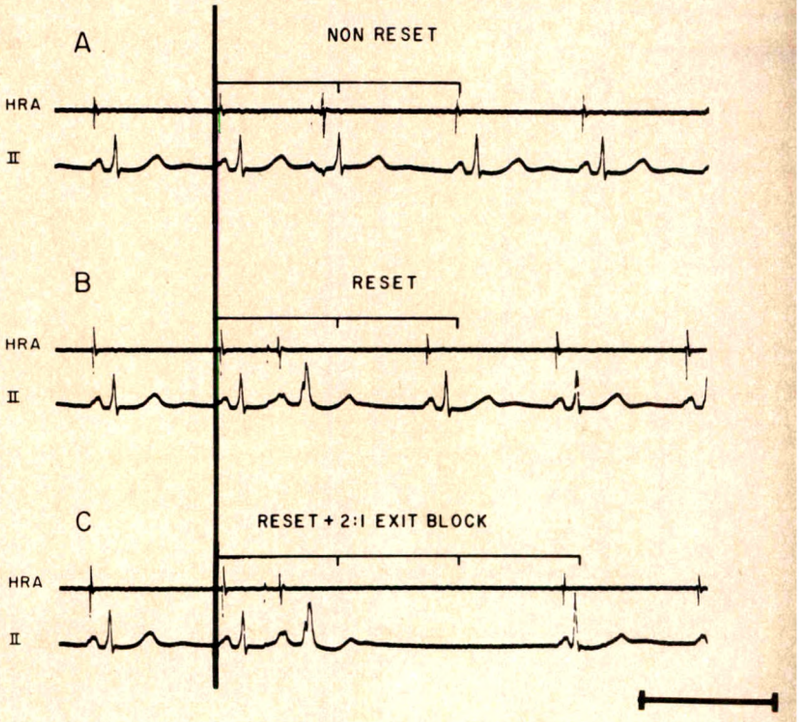

FIGURE 5. Lead II and high right atrial electrogram (HRA) during atrial premature stimulation. **Panel A,** nonreset of sinus node (points fall on the middle diagonal line in Figure 4). **Panel B,** reset of sinus node (points fall above the lower horizontal line but to the left of and below the middle diagonal line in Figure 4). **Panel C,** reset with 2:1 sinoatrial exit block (point falls above the upper horizontal line but to the left of and below the upper diagonal line in Figure 4). In each panel, the brackets represent a distance equal to the mean A_1-A_1 cycle length. In **Panel A,** A_1-A_2 plus A_2-A_3 equals two brackets and therefore equals two times $\overline{A_1\text{-}A_1}$. In **Panel B,** A_1-A_2 plus A_2-A_3 is less than two times $\overline{A_1\text{-}A_1}$. In **Panel C,** A_1-A_2 plus A_2-A_3 is one cycle length longer than in Panel B because of the lengthening of A_2-A_3 by a distance of approximately one $\overline{A_1\text{-}A_1}$. Time bar equals 1 second.

(Fig. 2). Only two pauses were terminated by beats of sinus origin. With a paced atrial cycle length of 500 msec, the postpacing pause was terminated by a junctional depolarization after 4,524 msec. With a paced atrial cycle length of 400 msec, the postpacing pause was terminated by a junctional depolarization without retrograde atrial conduction at 5,794 msec (Fig. 2, point C, and Fig. 3C). No atrial activity was seen until a junctional beat with retrograde atrial depolarization occurred after 10,920 msec. The sinus recovery time was therefore even greater than 10,920 msec.

Premature atrial stimulation: An estimated mean sinoatrial conduction time of 75 msec was calculated from the plot of A_2-A_3 versus A_1-A_2 (Fig. 4B). Rare recovery cycles demonstrating 2:1 sinoatrial exit block were again seen. The reference lines in this plot have the same meaning as in Figure 4A. Frames showing examples of nonreset, reset and 2:1 sinoatrial exit block after reset during atrial premature stimulation are shown in Figure 5.

Atrioventricular conduction: A-H and H-V intervals were again normal. A-H Wenckebach phenomenon occurred only with a paced atrial cycle length of 400 msec.

Discussion

Our patient clearly manifested several features of symptomatic sinus nodal dysfunction classically a part of the sick sinus syndrome.[2–7] Light-headedness, exertional dyspnea and supraventricular ectopic beats were all associated with inappropriately slow sinus rates as revealed by ambulatory monitoring. Provocative testing allowed further documentation and quantitation of the degree of sinoatrial dysfunction. Such testing[3,8–15] rests upon the principles of overdrive suppression by rapid atrial pacing, assessment of sinoatrial responses to atrial premature stimulation and manipulation of autonomic balance by pharmacologic means.

Sinoatrial recovery time: Gaskell[16] in 1884 first demonstrated the depression of intrinsic pacemaker rate that results from driving the heart at a rate faster than that of the dominant pacemaker. Further in vitro and in vivo support for overdrive suppression followed,[17–19] although the necessary and possible pacing frequencies varied from species to species. In recent years, the response of the sinus node to rapid atrial pacing has become one clinical method of provocative testing for sinoatrial dysfunction.[9,11,12,15] The length of time required for the sinus node to resume impulse formation after overdrive suppression—that is, the sinus recovery time—has been thought to reflect in large part the automatic properties of the node. However, conduction from the atrium to the sinus node during pacing and sinoatrial conduction after pacing must be considered in assessing the catheter-recorded postpacing recovery interval.

Values for the sinus recovery time have been described for normal persons and have been contrasted with those obtained in patients with sinus bradycardia or the sick sinus syndrome.[2,9,11,12,15] Unfortunately, the criteria for separating normal from abnormal values have varied. Rios et al.[15] found that the sinus recovery time averages 108 percent of the prepaced sinus rate in normal subjects and 113 percent in patients with the sick sinus syndrome, whereas Rosen et al.[3] stated that, in normal patients, cessation of rapid atrial pacing does not produce asystolic periods lasting 1.4 seconds. Narula et al.[11] first suggested correction of the sinus recovery time for heart rate. In 27 of 28 of their normal subjects, the value for sinus recovery time minus sinus rate, was 110 to 525 msec (15 to 59 percent of sinus cycle length). However, 16 of 28 patients with sinus bradycardia also had corrected sinus recovery times in this range. Mandel et al.[9] noted that 3 patients with the sick sinus syndrome had a longer sinus recovery time (4,732 ± 67 [standard error of the mean] msec) than did 43 normal subjects (1,041 ± 56 msec) and subsequently reported[12] that 29 of 31 patients with symptomatic sick sinus syndrome had a mean maximal postpacing pause of 3,164 ± 334 msec, whereas the normal mean was 1,073 ± 67 msec. In their normal subjects this represented a maximal pause of 106 to 128 percent of control sinus cycle length, the exact percentage depending on the pacing rate used. Ferrer's review[2] states that for a sinus cycle length of 1,000 msec a pause of 125 percent of the control cycle length is strongly suggestive whereas at sinus rates of 42 beats/min (a cycle length of 1,420 msec) a pause of 1,700 msec or more is diagnostic of sinus nodal dysfunction although this value is only 120 percent of the control cycle length. In our patient the maximal sinus recovery time in the control state was 2,632 to 3,325 msec, which is well in excess of 160 percent of the control sinus cycle length and exceeds any of the cited criteria of abnormality.

Sinoatrial conduction time: Estimation of sinoatrial conduction time by examining the sinoatrial response to premature atrial stimulation is also, in our opinion, useful in assessing sinoatrial function. Recent use of this principle stems from the observations of Langendorf et al.[20] on the behavior of sinus rhythm interrupted by atrial parasystolic beats and the subsequent application of these observations.[10,13,14,21–24] As with rapid atrial pacing, in vitro work has supported the principles and revealed some of the pitfalls of this technique.[25–27] Although the mean sinoatrial conduction time in our patient was only mildly prolonged when compared with values generally obtained at the same heart rate,[28] the documentation of 2:1 sinoatrial exit block indicates a severe disturbance of conduction.

Atropine: Provocative testing of sinus nodal function by pharmacologic means has been less extensively analyzed. Although considerable data exist concerning the response of normal subjects to graded doses of atropine,[22,29–38] only recently have the responses in patients with sinoatrial dysfunction been examined.[2,3,12,21,39,40] These responses suggest that a blunted acceleration in heart rate after administration of vagolytic agents indicates sinoatrial dysfunc-

tion. Mandel et al.,[12] for example, reported that after administration of 0.025 mg/kg of atropine the average increase in heart rate was only 23 percent (52 to 64 beats/min) in 31 patients with sinus bradycardia. Narula[39] found that 2 mg of atropine intravenously caused the sinus cycle length to decrease to less than 1,000 msec in only 3 of 75 patients with sinus bradycardia, and Rosen et al.[3] found that although 8 of 11 patients with symptomatic sinus node disease had an increase in heart rate of 25 to 125 percent after 1 mg of atropine intravenously, none had a sinus rate of more than 90 beats/min. Although our patient's sinus rate increased by 54 percent in response to 1 mg of atropine intravenously, a dose greater than those reported to induce a paradoxical sinus bradycardia[22,29–34,37,38,40] with an accompanying paradoxical increase in sinus recovery time,[22] this increase represented a peak post-drug rate of only 63 beats/min.

Far less has been written concerning the effects of vagolytic agents on the sinus recovery time and the mean sinoatrial conduction time. Engel et al.[21] and Mandel et al.[12] have stated that atropine can shorten a prolonged sinus recovery time, although Narula et al.[11] indicated that the sinus recovery time will not necessarily shorten to normal and suggested that nonsinus escape beats are more likely to terminate the postpacing pause after atropine. In view of the increased sinus rate and improved sinoatrial conduction seen in our patient in response to atropine, it seems surprising that rapid atrial pacing in the postmedication state resulted in significant lengthening of the postpacing pauses with markedly prolonged atrial quiescence on two occasions. In fact, similar although less dramatic findings have previously been reported on only one occasion to our knowledge.[41]

Mechanisms of paradoxical response to atropine: This seemingly paradoxical increase in the sinus recovery time after atropine may have resulted from: (1) alterations in sinus nodal automaticity, (2) alterations in sinoatrial conduction time, and (3) possible alterations in intra-sinoatrial nodal conduction. First, a primary change in sinus nodal automatic function must be important, although it is inseparably linked with alterations in sinoatrial conduction time. When the latter is decreased by atropine, there may be better penetration of the sinus node by atrial paced beats at any frequency of pacing than during the control state. If more paced impulses propagate to the sinus node per unit of time, sinus suppression might increase, thereby prolonging the sinus recovery time. This explanation assumes that (1) the mean sinoatrial conduction time is improved enough after administration of atropine to allow more atrial stimuli to reach the sinus node; (2) maximal sinus recovery time occurs at the atrial pacing rate that allows the maximal frequency of sinus nodal penetration per unit of time (which may not always be true); and (3) in spite of the increase in spontaneous automatic firing rate after administration of atropine, the sinus node remains highly sensitive to overdrive suppression of automaticity. If this latter assumption is true, it implies that sinus nodal suppression and sinus recovery time might be even more severely prolonged if the node were penetrated by an equivalent number of atrial impulses per unit of time before the administration of atropine, when the spontaneous firing rate was slower.

Second, a disturbance in sinoatrial conduction could explain the increase in sinus recovery time after administration of atropine. Since the sinoatrial junction functions somewhat analogously to the atrioventricular junction, disturbances in sinoatrial conduction can promote reentrant rhythms[42] in the perinodal fibers.[43] Reentrant beats have been demonstrated in the region of the sinus node in both animal[44,45] and human[46,47] studies, and concealed conduction in this tissue has also been noted.[48] There is no reason to believe, therefore, that repetitive concealed conduction such as has been shown to occur in the atrioventricular nodal region[49] could not occur in the sinus nodal region as well. It is thus possible that a reentrant rhythm in the perinodal fibers with concealed sinoatrial conduction, causing repetitive resetting of the sinus node but antegrade conduction block to the atria, could account for the apparently prolonged sinus recovery time in our patient after administration of atropine.

Third, it is known that conduction of impulses within the sinus node is relatively poor.[27,50] Conduction of impulses from the atrium to the sinus node is not necessarily associated with resultant depolarization of the entire node. Furthermore, the automatic properties of all P cells within the node are not identical. Therefore, the possibility exists that sinus impulse initiation after atrial premature stimulation or atrial pacing may not be by the same cell or at the same rate as existed before the atrial initiated beat. If intranodal conduction is influenced by vagotonia, then the possibility exists that such conduction could be enhanced by atropine, resulting in more uniform and complete depolarization of sinus nodal P cells when stimulated by an impulse arising in the atrium. This theoretical effect of atropine could conceivably enhance the suppression of sinus nodal automaticity by atrial pacing.

Clinical implications: Atropine may have therapeutic effects in patients with the sick sinus syndrome. It is capable of increasing sinus rate and improving sinoatrial conduction in some symptomatic patients, but in an as yet undetermined percentage of such patients, it may be potentially detrimental. As functional testing in our case demonstrated, the tendency to post-tachycardia asystole may be enhanced by the very agent proposed for therapy. Whether a prolongation of the sinus recovery time during provocative testing correlates precisely with the frequently observed period of severe bradycardia or asystole that may follow termination of spontaneous atrial tachyarrhythmias in the bradycardia-tachycardia form of the sick sinus syndrome has not yet been fully evaluated, but there is evidence that this is the case.[11,47] Regardless of the mechanism, an increase in

post-tachycardia bradycardia produced by atropine could increase the severity of symptoms in these patients. We therefore recommend that provocative electrophysiologic testing be repeated after potentially therapeutic pharmacologic agents are administered to patients with sinus nodal dysfunction since this may be the only means of demonstrating the possible detrimental effects of such therapy.

Acknowledgment

We are indebted to Dr. M. I. Ferrer for referring her patient for these electrophysiologic studies.

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Demand Pacemaker Arrhythmias Caused by Intermittent Incomplete Electrode Fracture

Diagnosis with Testing Magnet

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This report describes how the testing magnet was used to diagnose intermittent and incomplete electrode fracture in two patients with an implanted demand pacemaker. During fixed-rate pacing the interval between two consecutive pacemaker spikes intermittently doubled in length, suggesting that the pulse generator was continuing to fire on time into a transiently disrupted circuit. Attenuated pacemaker spikes occurring at the anticipated time of pacemaker discharge also provided a diagnostic clue. Ventricular electrograms from the defective electrodes registered small false signals.

The widespread use of demand pacemakers from a proliferating number of manufacturers has added a new dimension to clinical electrocardiography and has made the evaluation of pacemaker function increasingly difficult. This report describes use of a testing magnet to diagnose intermittent and incomplete electrode fracture in two patients with an implanted demand pacemaker. Such problems will undoubtedly become more frequent as the longevity of pulse generators continues to increase.

Case Reports

Case 1

The bundle of His in a 35 year old woman was surgically ligated because of intractable reciprocating supraventricular tachycardia in association with the Wolff-Parkinson-White syndrome.[1] Epicardial pacing electrodes were sutured on the diaphragmatic surface of the heart (one on the left and one on the right ventricle) and connected to a Medtronic bipolar demand pulse generator, model 5842. Pacing and sensing remained normal for about 20 months; about 22 months after implantation the patient was hospitalized because of the recent onset of syncope. The electrocardiogram revealed a complex pacemaker arrhythmia (Fig. 1 and 2).

Analysis of electrocardiograms (Fig. 1 and 2): The basic automatic interval (on demand) is 960 msec. The arrhythmia is characterized by:

1. *Irregular prolongation of the spike to spike (S-S) interval* to less than twice the automatic interval (960 to 1,460 msec). The S-S intervals of 1,080 and 1,120 msec (Fig. 2, bottom and top, respectively) suggest partial recycling of the pulse generator because they are significantly shorter than the sum of one automatic interval (960 msec) and the delivery (paced) refractory period of this pulse generator (that is, the earliest time after a pacemaker spike that sensing can occur—about 250 to 300 msec for this unit).[2,3]

2. *Apparent irregular prolongation of escape intervals.* The escape interval, conventionally measured from the onset of the surface QRS complex, may vary according to the pattern of ventricular depolarization, that is, time of sensing.[4] This slight variation is clearly shown in Figure 2, where beats with a narrow QRS complex (beats A) recycle the pulse generator with an escape interval of 980 to 1,000 msec, whereas Wolff-Parkinson-White beats with a broad QRS complex (beats B) initiate an escape interval of 1,080 msec (Fig. 1). However, the escape intervals seem to lengthen beyond the accept-

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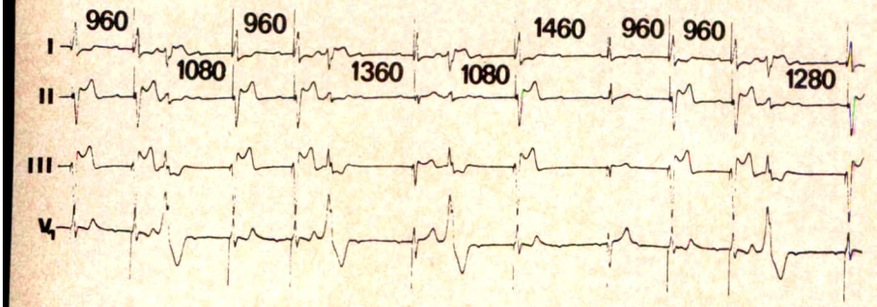

FIGURE 1. Case 1. **Top,** leads I, II, III and V_1 recorded simultaneously. **Bottom,** leads V_4, V_5 and V_6 recorded simultaneously. In this and subsequent figures the duration, in milliseconds, of the interval between two consecutive pacemaker spikes appears above the top tracing in each panel and the apparent duration, in milliseconds, of the escape intervals is indicated below the top tracing. The apparent escape intervals for beats B (Wolff-Parkinson-White beats with a broad QRS) range from 1,080 to 1,360 msec (3rd, 5th, 7th and 12th beats, top panel). See text.

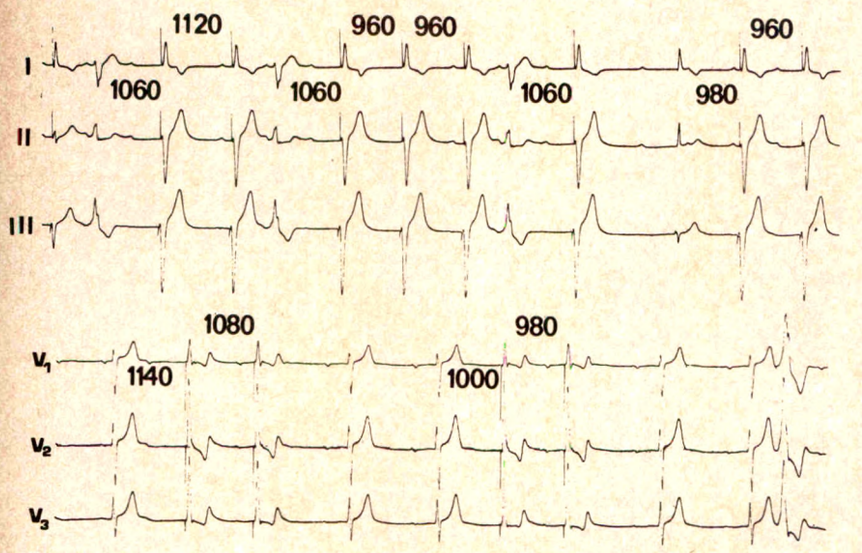

FIGURE 2. Case 1. **Top,** leads I, II and III recorded simultaneously on a day different from that shown in Figure 1. **Bottom,** leads V_1, V_2 and V_3 recorded simultaneously. The escape intervals for beats A (beats with narrow QRS) (third last beat, top panel, first and fifth beats, bottom panel) range from 980 to 1,140 msec. The S-S intervals of 1,080 and 1,120 msec suggest partial recycling of the pulse generator. See text.

able range; the escape intervals for beats A range from 1,080 to 1,360 msec (Fig. 1), whereas those for beats B range from 980 to 1,140 msec (Fig. 2).

3. *Irregular pauses after paced or spontaneous beats.* These pauses were shorter than two automatic intervals and were terminated by a spontaneous beat (Fig. 2). No cardiac cycles were lengthened to more than twice the duration of the automatic interval of the pulse generator.

Electrocardiograms were recorded for long periods with the magnet over the pulse generator (Fig. 3). The automatic interval was immediately shortened to 940 msec, a normal response for this pulse generator.[4] The amplitude of the pacemaker spike did not change with respiration, but the duration of the S-S interval doubled to precisely twice that of the automatic interval about once in every 50 pacemaker spikes. The 1,880 msec S-S intervals contained diminutive ineffectual pacemaker spikes (arrows) at the anticipated time of pacemaker discharge, that is, 940 msec after the last pacemaker spike (Fig. 3).

Multiple X-ray films of the pacing electrodes failed to reveal any fractures.

The pulse generator was surgically disconnected and electrograms were obtained from the pacing electrodes with the V lead of an electrograph (Siemens Mingograph, frequency response 400 hertz). The first electrode recorded a large ventricular electrogram free of artifact (Fig. 4, top); unipolarization of the pacing system, using this electrode as the cathode, resulted in normal sensing and pacing with a threshold of 2 milliamperes (tested with an external Medtronic pacemaker, model 5880). Electrograms from the second electrode (Fig. 4, bottom) revealed small artifacts (arrows), usually near the end of the T wave. Unipolarization, using this electrode as the cathode, reproduced the pacemaker arrhythmia previously seen, and the pacing threshold was 6.5 milliamperes.

A new pulse generator, model 5943, was then connected to the first electrode. The pulse generator that had been removed (model 5842) was suitably modified and used as an external pacemaker in another patient. No evidence of malfunction was noted, and this finding was subsequently confirmed by the manufacturers, who observed only the anticipated battery depletion for a generator of this age.

Case 2

An epicardial Medtronic demand pacemaker, model 5942, was implanted in a 63 year old man with complete

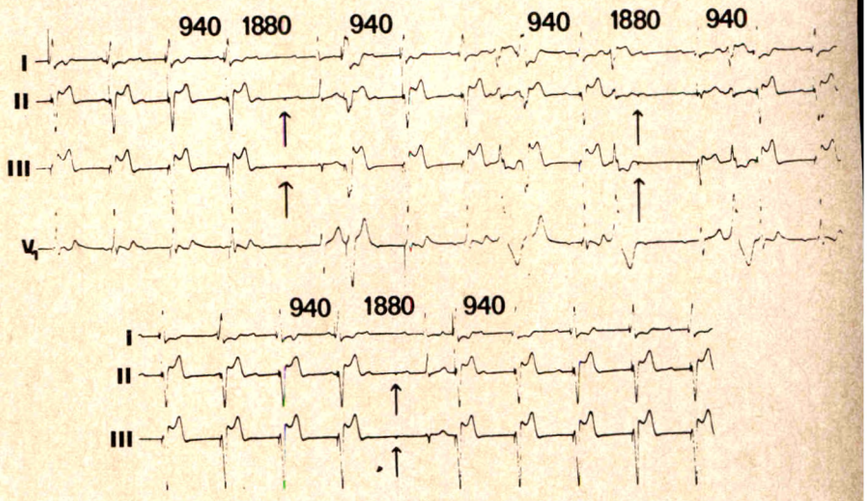

FIGURE 3. Case 1. Application of the magnet. **Top,** leads I, II, III and V_1 recorded simultaneously. **Bottom,** leads I, II and III recorded simultaneously. The S-S interval lengthens intermittently to precisely double the duration of the automatic interval. Note the occurrence of small ineffectual pacemaker spikes at the anticipated time of pacemaker discharge, that is, 940 msec after the last pacemaker spike **(arrows).** See text.

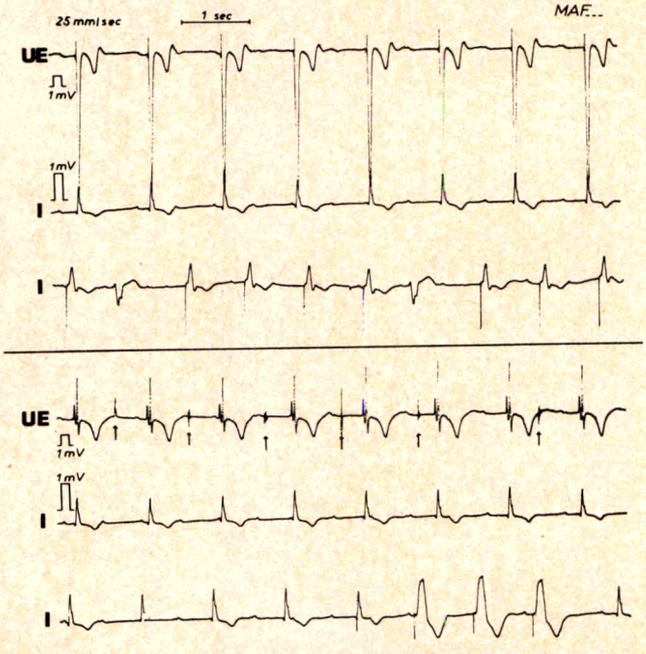

FIGURE 4. Case 1. **Top,** unipolar electrogram (UE) from the normal electrode recorded simultaneously with lead I **(middle strip).** The **lower strip** shows normal unipolar demand ventricular pacing with this particular electrode as the cathode. **Bottom,** unipolar electrogram (UE) from the defective electrode, recorded simultaneously with lead I **(middle strip).** Note the intermittent occurrence of false signals (1 to 3 mv) near the end of the T wave. The **lower strip** shows abnormal unipolar demand pacing by a Medtronic pulse generator, model 5943, when the defective electrode was the cathode.

atrioventricular block. Sensing and pacing with an automatic interval of 840 msec remained normal until 10 months after implantation when a routine electrocardiogram revealed intermittent prolongation of the S-S interval to 1,380 msec (Fig. 5). Deep respiration or change in posture did not significantly influence the size of the pacemaker spike in simultaneously recorded leads I, II, III and V_1.

These leads were then simultaneously recorded with the magnet over the pulse generator, but there was no evidence of malfunction during the recording of more than 1,500 paced ventricular beats; the S-S interval remained constant (about 830 msec) and the few observed spontaneous beats were consistently followed by a spike of normal size falling within the absolute refractory period of the heart (Fig. 6A, left panel). Further recordings with the magnet were obtained to observe the effect of critically timed spontaneous beats upon the size of the subsequent pacemaker spike. The pacemaker spikes of paced ventricular beats remained consistently normal in size during a recording of 5,000 beats, but the amplitude of the spike was strikingly diminished when it coincided with the T wave of some premature spontaneous beats (Fig. 6, A [right panel] and B to D). Note the complete disappearance of the pacemaker spike in Figure 6D with doubling of the S-S interval to precisely twice the length of the automatic interval.

Multiple X-ray films of the pacing electrode failed to reveal any fractures.

The pulse generator was surgically disconnected. The bipolar electrogram recorded intermittent small artifacts (arrows) related to the T wave (Fig. 7, top). Unipolar electrograms from the two electrodes were then recorded simultaneously (Fig. 7, UE1 and UE2). Electrograms from the first electrode displayed intermittent artifacts (UE1, arrows). Unipolarization of the pacing system using this electrode as the cathode revealed a pacing threshold of more than 25 milliamperes (tested with an external Medtronic pacemaker, model 5880). The electrogram from the second electrode (UE2) was entirely free of artifact. The pacing threshold was 1 milliampere when the system was unipolarized using the second electrode as the cathode.

A new unipolar Medtronic pulse generator, model 5943, was connected to the second electrode. The new system has functioned well during several months of follow-up. The pulse generator that had been removed, model 5942, was returned to the manufacturers, who found no evidence of malfunction.

Discussion

Abrupt changes in resistance within a pacing system produce corresponding voltage changes between the anode and cathode and may generate false signals that can be sensed by a demand pulse generator.[5–8] These signals generally occur at random and their presence should be suspected whenever demand pacing assumes a chaotic pattern as in Case 1. Case 2 illustrates how a defective electrode may induce rhythmic recycling of a demand pacemaker if mechanical systole creates false signals by making and breaking the circuit. The timing of such an abnormality would be electrocardiographically indistinguishable from T wave sensing.

Factors affecting amplitude of pacemaker spike: Barring small physiologic variations with respiration, the amplitude of the pacemaker spike in a bipolar pacing system may diminish in the following circumstances: (1) Pulse generator failure, which was ruled out in both cases. (2) Short circuit between the electrodes, which was excluded by the electrographic recordings and successful conversion to long-term unipolar pacing. (3) Defective electrode insulation. The size of the pacemaker spike is a function of the distance between the electrodes and the current density. Because an insulation break creates an alternative

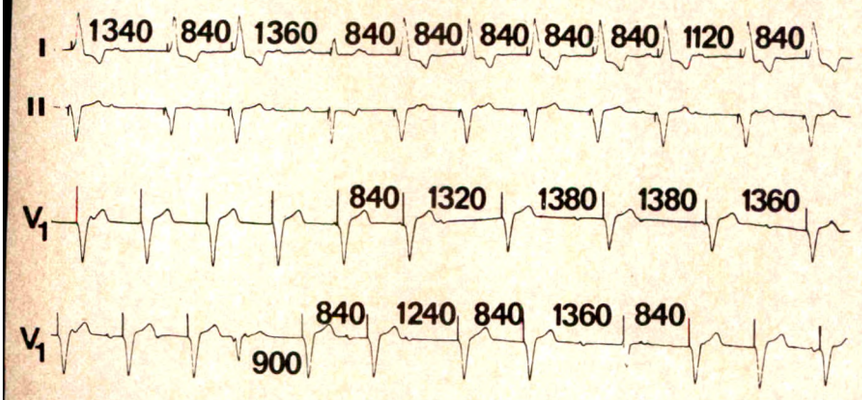

FIGURE 5. Case 2. Leads I and II recorded simultaneously. The S-S interval lengthens intermittently from 840 msec (automatic interval) to a value never higher than 1,380 msec. The **bottom strip** shows normal sensing of a spontaneous beat by the pulse generator.

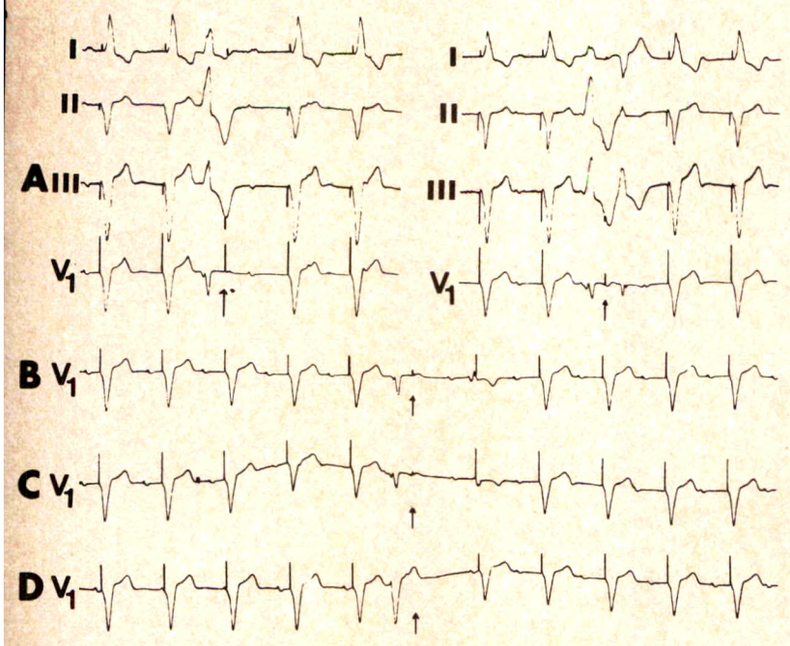

FIGURE 6. Case 2. Application of the magnet causes a slight shortening of the automatic interval to about 830 msec.[4] **A,** leads I, II, III and V_1 recorded simultaneously. In the left panel there is no evidence of pacemaker malfunction. The third pacemaker spike is normal in amplitude and falls within the refractory period of the heart. In the right panel, note the reduced size of the third pacemaker spike, also falling within the refractory period of the heart. **B to D,** lead V_1. Various reductions in spike amplitude after spontaneous beats **(arrows).** In **D,** duration of the S-S interval increases to precisely twice that of the automatic interval, and the pacemaker spike disappears. Generalized reduction of the pacemaker spike was also seen in leads I to III (not shown) recorded simultaneously with lead V_1.

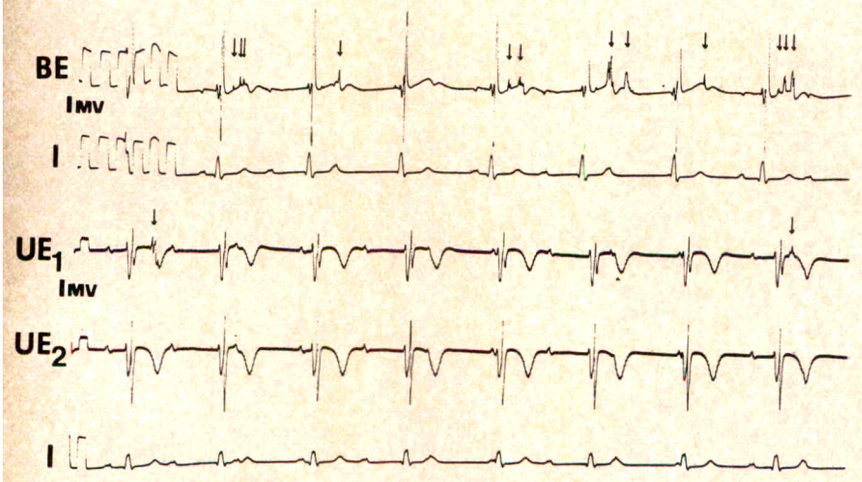

FIGURE 7. Case 2. **Top,** bipolar electrogram (BE) and surface lead I. **Bottom,** simultaneous recording of unipolar electrograms from the two electrodes (UE_1 and UE_2) and surface lead I. Note the small artifacts at the **arrows.** Calibration = 1 mv.

path for current flow,[9] the electrical dipole of the leakage current from a small insulation defect close to the proximal electrode could theoretically reduce or cancel the resultant dipole and therefore the amplitude of the pacemaker spike. Clinically, however, insulation defects in bipolar systems almost invariably increase the amplitude of the pacemaker spike,[10,11] making this possibility highly unlikely but not altogether impossible in our two cases. (4) A partial wire fracture with a fluid bridge.

Testing magnet for diagnosing intermittent partial electrode fracture: The testing magnet for contemporary pacemakers is valuable in the evaluation of pacemaker function because its use eliminates all arrhythmias related to oversensing.[12] This report shows how the magnet may also be used to diagnose intermittent partial electrode fracture. In this situation, long electrocardiographic records are essential because firing of the pulse generator must coincide with the momentary increase in electrode resistance. Pacemaker spikes usually disappear in the presence of an electrode fracture but the attenuated spikes so clearly seen in Figures 3 and 6 provided a striking and relatively uncommon diagnostic clue of a transient increase in electrode resistance.

When the magnet was placed over the pulse generator, the S-S interval intermittently lengthened to precisely double the duration of the automatic interval in contrast to its irregular prolongation during demand pacing. During fixed-rate pacing (that is, while the magnet is being used), pacemaker pauses that are exact multiples of the automatic interval suggest that the pulse generator is continuing to fire on time into a transiently disrupted circuit.[13] When the spontaneous rhythm is faster than the preset rate of a demand pacemaker this finding may be the only diagnostic clue to intermittent electrode fracture because false signals will remain undetectable.

The electrogram from the defective electrodes registered small false signals of borderline voltage for sensing.[14] Although these relatively small signals may partially recycle contemporary implantable Medtronic pulse generators,[3] it is unlikely that they were responsible for the shortened escape interval after paced beats in Figure 2 because interruption of the pacing circuit shortly after a pacemaker spike disturbs the high residual polarization voltage at the myocardial-electrode interface and generally creates much larger signals.[4,13] The signals responsible for partial recycling after a paced beat probably were quite large but fell within the relative refractory period of the pulse generator (the short recovery period after the delivery refractory period) when comparatively larger signals may also partially recycle an implantable Medtronic pulse generator.[2,4,13] This possibility reemphasizes the importance of fully understanding the specifications of normally functioning pulse generators since seemingly erratic behavior may not necessarily indicate failure.

Sensing of concealed ventricular extrasystoles: Massumi et al.[15] recently suggested that a demand pacemaker could sense intracardiac voltage generated by concealed ventricular extrasystoles (depolarization confined to the His-Purkinje system and invisible in the 12 lead electrocardiogram[16]). Several authors[17–19] have since accepted this concept despite cogent alternative explanations[8] for these observations. The electrocardiograms in our report resemble those described by Massumi et al.[15] and, in this context, spurious signals recorded from defective electrodes should not be interpreted as originating from the heart. The concept of sensed concealed ventricular extrasystoles should remain speculative and highly improbable on electrophysiologic grounds; consideration of this possibility in the differential diagnosis of a complex pacemaker arrhythmia might detract attention from a potentially more serious problem such as an intermittent electrode fracture.

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Etiology of the Mitral Valve Prolapse-Click Syndrome

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The syndrome of mitral valve prolapse with associated auscultatory and electrocardiographic findings has recently generated considerable interest.[1–25] Its frequency has been documented in several large series.[1–3,8] Ours currently stands at 200 patients, with angiographic confirmation of the mitral valve prolapse in 60. Two main theories have been advanced to explain the etiology of this syndrome: The first stresses mitral valve abnormality and the second, myocardial involvement as demonstrated by left ventriculography and hemodynamic studies.

1. The Valvular Theory

According to this theory, myxomatous degeneration of the mitral valve is the underlying mechanism responsible for the mitral valve prolapse.[2,3,15,16,21] The loss of the normally dense collagenous supporting structure allows stretching of the cusps by normal ventricular pressure and results in redundant and ballooned leaflets. Fibrous friction lesions of the left ventricular endocardium with adhesions of the chordae tendineae and collagenous prolongation into the subjacent myocardium have been described.[23] Papillary muscle fibrosis in the absence of coronary atherosclerosis has been demonstrated.[3,24] In all but one reported series,[1] rheumatic heart disease was not evident.

The valvular theory attempts to explain the various manifestations of the click syndrome. The chest pain is thought to be due to excessive stretching of the papillary muscles.[1,3,25] According to the Laplace law, the chordae tendineae, attached to a voluminous billowing leaflet that by overshooting the other leaflet no longer has its support, are under increased tension. Such forceful traction on the papillary muscle interferes with its rather tenuous vascular supply and may produce papillary muscle and subendocardial fibrosis. The electrocardiographic changes and the ventricular arrhythmias are secondary to papillary muscle and endocardial ischemia and subsequent fibrosis. Sudden death is believed to be arrhythmic in origin. The click, which coincides with maximal prolapse,[26] is probably due to "sudden tensing of the everted valve leaflets," the "snapping of a sail" phenomenon.[27] The late systolic murmur is attributed to the initially competent valve becoming incompetent as prolapse develops.[26,28] Response of the click and murmur to various maneuvers is explained by changes in the left ventricular volume.[3] The sharp systolic retraction seen in apex cardiograms is ascribed to abnormal tension on the papillary muscle resulting in the base of the muscle being drawn inward.[2,6] The indentation along the inferior border of the left ventricle[29] may be due to the same mechanism.[3]

Pathologic changes in mitral valve: In several recent reports, myxomatous degeneration was demonstrated in patients who had midsystolic clicks. Altogether, nine cases of this association have been documented,[5,7,14,17,30–32] including a recent case observed by our group and two cases kindly reported in a personal communication from Edwards and Guthrie.[32] To my knowledge, these nine cases represent the only available adequate pathologic studies in patients with nonejection clicks. Their importance lies in the demonstration of redundant myxomatous cusps in each instance. Despite the absence of oculoskeletal manifestations, Read et al.[15] have ascribed myxomatous degeneration of the mitral valve to a forme fruste of Marfan's syndrome. At present, there is no evidence to warrant such generalization.[3]

2. The Myocardial Theory

This theory is based primarily on angiographic and hemodynamic findings without pathologic correlations. Although some workers have implicated coronary artery disease,[33,34] most advocates of the myocardial theory have postulated a cardiomyopathy unrelated to this disease. Their disparate findings are as follows:

1. *Abnormal systolic protrusion of the inferior aspect of the left ventricle.*[29] This results in elevation of the papillary muscles; the chordae tendineae become slack, allowing the posterior leaflet to balloon into the left atrium.

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· 2. *Noncontraction or late systolic expansion of the inflow tract of the left ventricle* with significant reduction in the extent and mean velocity of fiber shortening in this segment.[9] The same group[11] has reported congenital absence of the atrioventricular (A-V) groove branch of the left circumflex coronary artery, postulating that this absence may be responsible for the segmental myocardial dysfunction.

3. *Left ventricular asynergy.* Gooch et al.[8] have described asynergistic contractions or relaxations in 17 of their patients; 16 had an anterior convex bulging during late systole or early diastole, and eight of these also had systolic bulging of the inferoposterior wall of the ventricular cavity. One patient had apical akinesia. The same group[10] have subsequently described five types of abnormal left ventricular systolic contraction patterns: (a) "ballerina foot" pattern (vigorous posteromedial contractions with anterior convexity); (b) "hourglass" pattern (vigorous ring-like traction involving the middle portion of the left ventricle); (c) inadequate shortening of the long axis; (d) posterior akinesia; and (e) pattern of cavity obliteration.

4. *Hemodynamic disturbances.* We have described a constrictive pattern of the left ventricular pressure curves in 5 of our original 32 cases.[25] In the absence of severe mitral regurgitation, hemodynamic studies have generally shown no abnormalities.[3,10] However, Gulotta et al.[35] reported in 20 of their 26 patients left ventricular dysfunction documented by either elevated left ventricular end-diastolic pressure, low resting cardiac index or inappropriate rise in cardiac index during exercise.

3. Critique of the Myocardial Theory

A. Relation between coronary artery disease and the mitral valve prolapse-click syndrome: Papillary muscle dysfunction resulting from coronary artery disease has been held by a few workers[33,34] to be responsible for this syndrome. I believe this represents a coincidental rather than causal association of two common diseases.[3,13,36] We have observed only four instances of proved coronary artery disease in 45 of our patients who underwent coronary cinearteriography (mild to moderate coronary stenosis in two patients and severe stenosis in two). Other authors[3,8–10,30] have reported on the results of selective coronary arteriography in more than 200 patients and have documented coronary artery disease in only 2 to 3 percent. Furthermore, since October 1971, the date of publication of the article by Steelman et al.[33] we have been searching for midsystolic clicks among patients admitted to our coronary care unit (approximately 700 patients annually). We encountered no patients who manifested clicks de novo in the course of acute myocardial infarction. A click was heard in only six patients, four of whom underwent cardiac catheterization; mitral valve prolapse was demonstrated in all and coronary artery disease in only two. Late systolic murmurs can be due to papillary muscle dysfunction,[37–39] but it must be proved that midsystolic clicks as such can be caused by this disorder, an association that is not evident in three comprehensive reviews of papillary muscle disease.[37–39] It is unfortunate that some cardiologists, including the authors of a well respected textbook,[40] have accepted the unproved concept of causal linking between coronary artery disease and the click syndrome. The available evidence does not warrant suspicion of coronary artery disease when a click is heard and supports the converse view, that the finding of a click in a patient with atypical chest pain and ST-T wave changes makes coronary artery disease unlikely.

Review of the coronary arteriograms in our 45 patients revealed congenital absence of the A-V groove branch of the left circumflex artery[9] in only 8 patients, 7 of whom had a large posterolateral branch of the right coronary artery to compensate for this absence.

B. Nonischemic cardiomyopathy: The angiographic abnormalities range from akinesia[9] to hypercontractility,[10,29] from hypokinesia of the inferior wall[9] to abnormal systolic protrusion of the same wall[29] and from asynergy of the anterior wall with systolic bulging[8,35] to vigorous contraction involving the same area.[10] To explain these contradictory findings disparate causes of the same syndrome have to be postulated, thus prompting a search for an explanation for these discrepancies. The angiographic abnormalities may be factitious and due to the effect of premature ventricular contractions induced during the injection of dye.[41] In one of our patients who underwent two angiographic studies 4 years apart, marked asynergy associated with a run of premature ventricular contractions was noted during the first study but not during the second study, which was free of arrhythmias. Even if one assumes that abnormalities of the left ventricular contraction are genuine, they do not necessarily indicate a primary myocardial disease. Rigidity of various segments of the left ventricle, particularly near the inflow tract, may be due to fibrotic friction lesions[23]; fibrosis of the papillary muscles and adjacent endocardial areas resulting from excessive traction may explain localized akinesia or hypokinesia. Excessive contractility may be due to aneurysmal ballooning of the easily distensible cusps reducing the volume of blood encompassed by the muscular element; this would mimic the effect of mitral insufficiency, decreasing myocardial afterload and increasing the velocity and extent of fiber shortening.[42] The sum of all these factors may result in a spectrum of angiographic manifestations.

The hemodynamic disturbances, when present, may be due to endocardial, subendocardial and papillary muscle ischemia and fibrosis. The decreased compliance would explain the "constrictive" pattern.

4. Future Directions

Implicating myxomatous degeneration of the mitral valve as the underlying mechanism in this syndrome poses further etiologic problems. The main

question to be solved is: What is myxomatous degeneration? What causes it? Shift of emphasis from the myocardial to the valvular theory would focus attention on this pathologic abnormality and the nature of mucopolysaccharide infiltration. Only in a few reported cases[3,19,20] was this syndrome found to be genetically determined. No definite correlation with age was demonstrated by Pomerance,[21] who suggested a nonspecific tissue reaction resulting from many possible etiologic processes.

Gross and microscopic studies are needed to elucidate the etiology of the click syndrome and to confirm the valvular theory of myxomatous degeneration. Since coronary artery disease does not induce myxomatous degeneration, the demonstration of a nonejection click in a patient with coronary artery disease and a nonmyxomatous mitral valve would be the only convincing evidence linking these two entities.

In conclusion, the mitral valve prolapse-click syndrome can be termed an entity in search of a raison d'être. It is my contention that further research into the nature of the myxomatous process is, to quote Sutton's law, "where the money is."

Addendum

After submission of this editorial, Cobbs and King reported a case of mitral valve prolapse with "abnormal inward motion at the site of the posterior papillary muscle" (Cobbs BW, King SB: Mechanism of abnormal ventriculogram and ECG associated with prolapsing mitral valve [abstr]. Circulation 49, 50 Suppl III:III-7, 1974). Mitral valve replacement was carried out for intractable ventricular arrhythmias and one episode of ventricular fibrillation. Postoperatively, the left ventriculogram promptly returned almost to normal. This interesting case adds further support to the valvular theory and disproves theories postulating an abnormal contraction ring.[9,10]

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Left Ventricular Volume Measurement by Echocardiography: Fact or Fiction?

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Measurement of left ventricular volume in man necessitates certain assumptions regardless of the method used. These assumptions tend to be forgotten as the method grows in popularity. Even though the originators of the technique of echocardiographic volume measurement admitted the inaccuracies in their assumptions, echocardiography is currently an accepted method for measuring ventricular volume. It is appropriate, therefore, to reevaluate critically this original and widely used technique and to emphasize not only the original assumptions but also the many problems that heretofore may not have been considered by the clinician.

Possible Errors in Echocardiographic Measurements

The clinical applications of reflected ultrasound for volume measurement as performed by simultaneously visualizing the interventricular septum and the left ventricular posterior wall have been described by several investigators.[1–6] However, they disagree on the anatomic correlate of this measurement. Feigenbaum,[1,5] Popp[2] and Murray[6] and their co-workers have stated empirically that these measurements represent an oblique section through the left ventricle. Pombo et al.[3] and Fortuin et al.,[4] on the other hand, have presented evidence that the echocardiographic measurement represents the left ventricular minor axis. The probable answer to this seeming paradox is that ultrasound is not measuring the same dimension in all patients.

Errors in measuring minor axis: The geometry of the left ventricle, the size and shape of the mitral leaflets, the orientation of the left ventricle within the chest cavity and the location of the acoustical window vary. Although these landmarks allow the echocardiographer to measure the same dimension in the same patient from day to day, individual differences can result in deviations from the "ideal" measurement in both the longitudinal and transverse directions. With use of a simplified geometric model of the left ventricle within the chest cavity (a model that, because of its geometric regularity, minimizes the effect of any deviation), it can be calculated that a 10° or 1 cm discrepancy between the ultrasonic beam and the minor axis can result in a 5 to 10 percent error in measurement of the minor axis. This is an even greater problem in ventricles that are larger and more spherical than normal: First, as a ventricle enlarges, its major axis becomes longer, and the true minor axis is displaced apically away from the tips of the mitral valve leaflets. Second, an oblique chord through an ellipse is more likely to approximate its minor axis than a chord through a sphere is likely to approximate its diameter. When the erroneous single dimension is extrapolated to three dimensions and when these measurements are applied to stroke volume determination, this error becomes most significant.

Errors in measuring distance: Assuming, though, that it is possible to standardize measurement of the minor axis, we must next consider the error involved in making any echocardiographic measurement of distance. One measures distances with ultrasound by assuming that the distance from the transducer to an object is proportional to the time it takes for the beam to be reflected back from the object to the transducer. Because there is a random error in transmission velocity through a nonhomogeneous medium and because measured distance is a function of transmission "time," there is a random error in distance measurement that varies directly with the distance measured. It is obviously impossible to define exactly the magnitude of this error. For example, even if this error is only ±1 percent of the distance, then (also allowing for the 0.1 cm resolution) the approximately 5 cm distance between the transducer and the interventricular septum would

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have an error of ±0.15 cm. If the distance to the posterior wall is 10 cm, the error is ±0.2 cm. Because these errors are random, they are added when the distances are subtracted, and the echocardiographic dimension becomes 5 ± 0.35 cm. (If it were possible to place the transducer on the interventricular septum, then the dimension would be 5 ± 0.15 cm.) The greater the distance from the chest wall to the heart (for example, in patients who are obese or who have chronic obstructive pulmonary disease), the greater is the error associated with this method of measurement. These error brackets must, of course, be added to the problem of locating the "right" dimension.

Errors in translating minor axis dimension into volume determination: If the left ventricular minor axis is known, is it possible to translate this linear dimension into a three-dimensional volume? It is possible if the following assumptions are true: (1)

TABLE I

Comparison of Methods for Calculating End-Diastolic (EDV) and End-Systolic (ESV) Volumes from the Appropriate Ultrasonic Dimensions (Ud and Us)

Reference*	EDV vs. Ud	r	P	SEE	ESV vs. Us	r	P	SEE
Pombo et al.[3]	$EDV = 0.962\ Ud^3 + 11.53$	0.97	<0.01	27.76	$ESV = 1.041\ Us^3 + 6.25$	0.97	<0.01	23.64
Fortuin et al.[4]	$EDV = 59\ Ud - 153$	0.83	<0.001	36	$ESV = 47\ Us - 120$	0.84	<0.001	26
	$EDV = 0.704\ Ud^3 + 28.1$	0.84	...	70	$ESV = 0.793\ Us^3 + 0.65$	0.84	...	44
Feigenbaum et al.[5]	$EDV = 0.922\ Ud^3 + 72.42$	0.895	<0.001	55	$ESV = 0.96\ Us^3 + 42$	0.809	<0.001	43
Murray et al.[6]	$EDV = 53.9\ Ud - 154.5$	0.79	...	...	ESV vs. Us	0.66	...	...
	ESV vs. Ud^3	0.81	...	...	ESV vs. Us^3	0.65	...	...

* All authors reported statistically significant relations. Murray et al. did not derive regression equations for EDV vs. Ud^3, ESV vs. Us or ESV vs. Us^3. Feigenbaum et al. derived, but did not report, a regression equation for ESV vs. Us^3; the equation listed was derived from their data.

d = end-diastolic; s = end-systolic; *P* = probability; SEE = standard error of the estimate; U = left ventricular axis measurement by echocardiography.

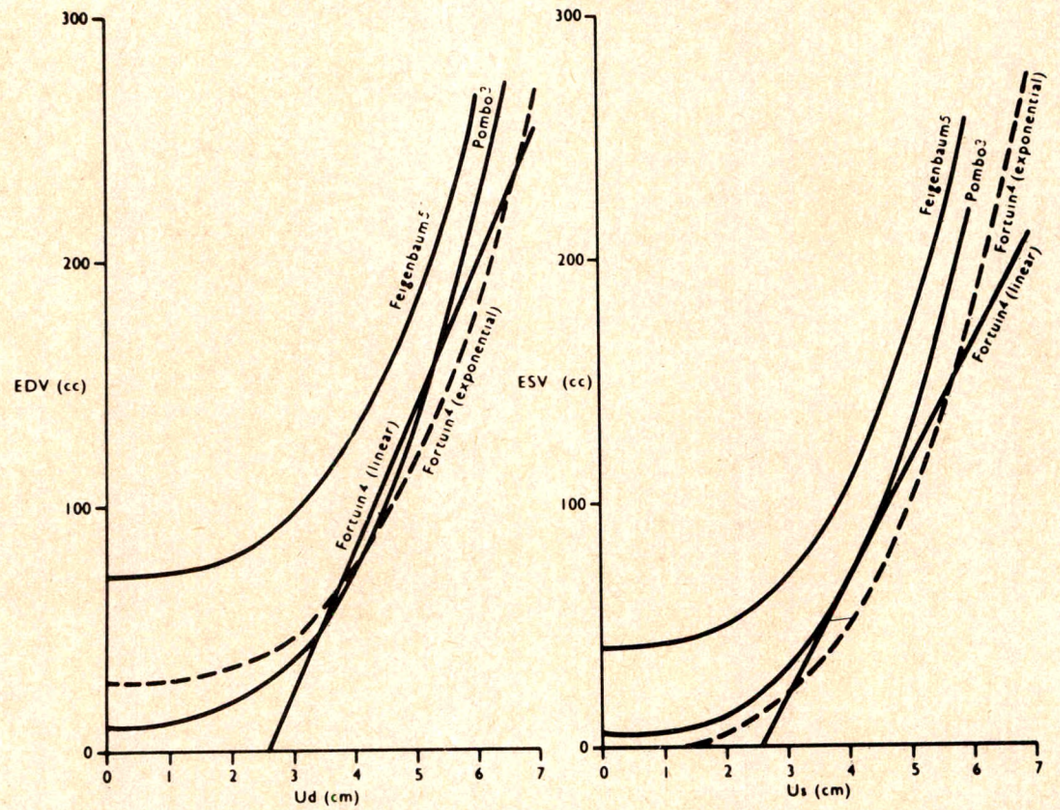

FIGURE 1. Graphic representation of the formulas of Table I. The regression equation of Murray et al.[6] for end-diastolic volume (EDV) vs. Ud is similar to that derived by Fortuin et al. (linear) and is not represented separately. For any given left ventricular axis measurement in diastole (Ud) or systole (Us), there is a whole range of formulas and volumes from which to choose.

that the longitudinal cross-sectional geometry of the left ventricle is known and is the same in all persons (present thinking assumes it to be an ellipse); (2) that its three-dimensional shape is this two-dimensional figure rotated on its major axis (that is, an ellipsoid of revolution in which all longitudinal cross sections are the same); (3) that these two conditions are true in both systole and diastole, in volume overload and in pressure overload states, in ischemic heart disease and in primary myocardial disease; and (4) that the major axis of the left ventricle is constant or is a constant known multiple of the minor axis in all patients in systole and in diastole. Unfortunately, none of these assumptions are true—especially the last, and especially within the large group of patients with coronary heart disease.

Certain known facts about ventricular geometry are applicable to this situation. Normal ventricular

TABLE II

Equations Proposed to Calculate Stroke Volume (SV) from Echocardiographic Dimensions (Ud-Us)

	SV vs. (Ud-Us)	*r*	*P*	SEE	EF vs. $\left(\frac{Ud-Us}{Ud}\right)$	*r*	*P*	SEE
Pombo et al.[3]	$SV = 1.16\,(Ud^3-Us^3) - 23.3$	0.83	<0.01	25.5	$EF = 1.47\left(\frac{Ud^3-Us^3}{Ud^3}\right) - 0.29$	0.80	<0.01	0.09
Fortuin et al.[4]	$SV = 1.54\,(59Ud-47Us) - 33$ $SV = 1.54\,(EDV-ESV) - 50.8$	0.77	...	18	$EF = 1.3\left(\frac{Ud-Us}{Ud}\right) + 0.25$	0.79	<0.001	0.07
	$SV = 0.63\,(Ud^3-Us^3) + 26.9$	0.83	...	37	$EF = 1.19\left(\frac{Ud^3-Us^3}{Ud^3}\right) + 0.08$	0.81	...	0.07
Feigenbaum et al.[5]	$SV = 0.777\,(Ud^3-Us^3)$	0.71	<0.001	34	...	...	...	...
Murray et al.[6]	$SV = 175.4\,(Ud-Us) - 137.1$	0.90	...	...	$EF = 3.13\left(\frac{Ud-Us}{Ud}\right) - 0.09$	0.69	...	...
	$SV = 35.1\,(Ud-Us)^3 + 3.64$	0.97	...	...	...	...	...	...

The linear formula of Fortuin et al.[4] was based on their formulas for end-diastolic and end-systolic volume, and is shown in terms of these variables and in terms of U.

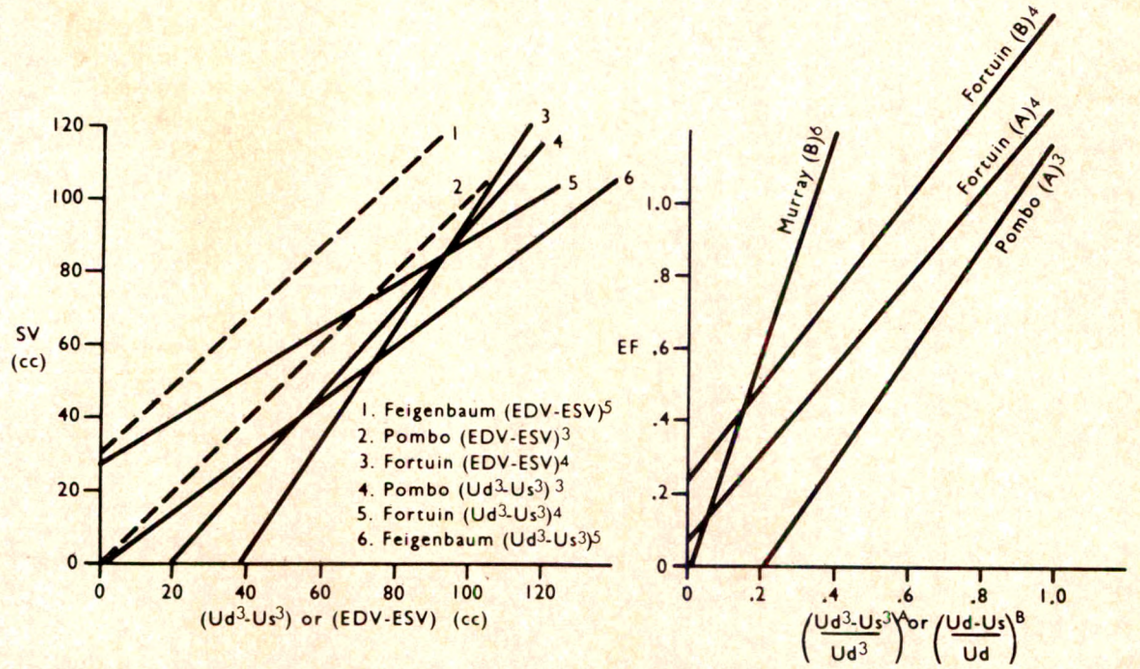

FIGURE 2. Graphic representation of the various formulas for calculating stroke volume (SV) and ejection fraction (EF). **A,** also shown are graphs that are derived if stroke volume = end-diastolic volume (EDV) minus end-systolic volume (ESV) according to the equations for EDV and ESV published by Feigenbaum et al.[5] and Pombo et al.[3] This is analogous to the method used in angiographic calculations and, although not strictly comparable, serves to demonstrate further the inaccuracy and inconsistency of the ultrasonic method. The formula of Murray et al.[6] is not plotted because $(Ud-Us)^3 = Ud^3 - 3Ud^2Us + 3UdUs^2 - Us^3$ and, therefore, cannot be compared with $Ud^3 - Us^3$. **B,** the ejection fraction formulas of several authors who used either $(Ud^3 - Us^3)/Ud^3$ (called A) or $(Ud - Us)/Ud$ (called B). Because of the different exponents involved, it is impossible to compare "A" and "B" equations.

shape *does* approximate an ellipsoid of revolution. As it enlarges, a ventricle becomes more spherical. During ejection, the left ventricle becomes more spherical. During ejection, the left ventricle does not contract concentrically. The minor axis shortens 10 to 35 percent while the major axis shortens by only 1 to 5 percent.[7] At end-systole the ratio between the major axis and the minor axis is greater than at end-diastole. As the ventricle enlarges, the minor axis enlarges more than the major axis, and the ratio between the two axes becomes less.

Correlation of Echocardiographic and Angiographic Measurements

Despite these problems, four studies[3–6] have reported statistically significant correlations between the ultrasonic left ventricular axis (U) and left ventricular volume. Pombo et al.[3] assumed that the major axis is twice the size of the minor axis in all patients in systole and in diastole. They then related left ventricular volume to U^3. Feigenbaum et al.[5] also used U^3 because of its statistical superiority over U^2 or U. Fortuin et al.[4] compared the ventricular volume with U and U^3 and demonstrated similar statistical correlation with both U and U^3 in normal-size ventricles but better correlation with U in larger ventricles. Murray et al.[6] were not able to demonstrate a statistically significant difference. Table I and Figure 1 compare the findings of these investigators. The wide variations in the regression formulas derived from their data indicate the extent to which their results differ. To emphasize this point further, if all the data reported in these four studies were plotted on the same graph, an echocardiographic diastolic dimension of 5 cm would be associated with angiographic volumes of 125 to 250 cm^3 and an end-systolic dimension of 4 cm would be associated with angiocardiographic volumes of 50 to 150 cm^3. Similarly, normal angiocardiographic volumes were reported in patients who had abnormally small, normal or abnormally large echocardiographic dimensions.

The scatter of angiographic volumes associated with any given ultrasonic dimension increased as the dimension increased. This is consistent with our two previous considerations. The difficulty in standardizing the echocardiographic dimension increases as the ventricle becomes larger, and the error of measurement becomes larger as the ventricle enlarges. Just as the linear dimension is cubed to calculate volume, the error is also cubed. A dimension of 5 ± 0.35 cm becomes a volume of 125 ± 29 cm^3, a dimension of 6 ± 0.4 cm becomes a volume of 216 ± 46 cm^3 and a dimension of 7 ± 0.45 cm becomes a volume of 343 ± 73 cm^3. Once these error brackets are applied to volumes as predicted by the various regression formulas (Fig. 1), the possible range of volumes becomes huge. Accurate predictions are therefore impossible.

These considerations become even more important when applied to the determination of stroke volume and cardiac output. If it is impossible to predict accurately end-diastolic and end-systolic volume, it must be impossible to predict stroke volume by this method. Table II and Figure 2 demonstrate the published formulas for calculating these variables.

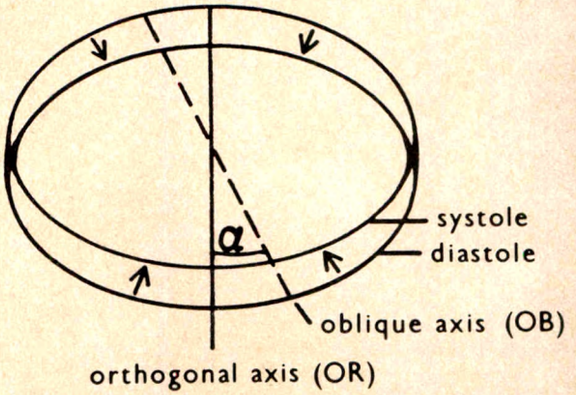

FIGURE 3. Relation of oblique section through the left ventricle (oblique axis) and the true left ventricular minor axis (orthogonal axis). Because the ejection fraction is a measure of the relative extent of shortening of the minor axis, ultrasound can accurately measure this variable. Furthermore, standardizing the ultrasonic measurement among individual patients is less important when measuring the ejection fraction. The oblique axis, the orthogonal axis and the constant angle approximate congruent triangles at end-diastole and at end-systole. As a result, the relative shortening of the oblique axis does accurately reflect the relative shortening of the orthogonal axis.

Clinical Status of Echocardiography

Following the clinical course: Where, then, is the place of ultrasound in measuring left ventricular volume and pump function? Because echocardiography can reproduce the same measurement in the same patient, it is most useful for following the clinical course of individual patients. For example, we have used echocardiography to follow changes in volume during atrial pacing; the absolute dimensions and the degree of shortening during contraction decrease at faster heart rates. When angina develops, the dimension increases, and the extent of shortening decreases even more. Premature ventricular contractions have smaller dimensions, and the postextrasystolic beats have larger diastolic and smaller systolic dimensions.

Similarly, the course of a patient with a myocardial infarction could be followed. A patient with recurrent chest pain of unknown cause could be studied to see whether the expected changes in ventricular size that accompany angina pectoris are manifest. The response of a patient to pharmacologic intervention could be evaluated objectively since many drugs (digitalis, diuretic agents, propranolol and nitroglycerin, for example) are effective because of their influence on ventricular volume. Also, pre- and postcoronary revascularization ventricular dimensions could be measured in all patients, and the occurrence of graft closure could be inferred because of deteriorated ventricular function even though the patient remained asymptomatic.

Left ventricular ejection fraction: The other use of echocardiography may be in measuring left ventricular ejection fraction (EF). Because contraction is a function of minor axis shortening:

$$EF = \frac{EDV - ESV}{EDV}$$

$$EF = \frac{\pi/6\ (Dd^2L) - \pi/6\ (Ds^2L)}{\pi/6\ (Dd^2L)}$$

$$EF = \frac{Dd^2 - Ds^2}{Dd^2}$$

where EDV is end-diastolic volume; ESV is end-systolic volume; Dd is the end-diastolic minor axis; Ds is the end-systolic minor axis, and L is the major axis. Therefore, it is *not* necessary to be able to measure volume in order to measure ejection fraction. More importantly, because the ejection fraction represents a relative shortening of the minor axis, it is not necessary to standardize the echocardiographic measurement. As shown empirically in Figure 3, an oblique section through the left ventricle maintains a constant ratio to the true left ventricular minor axis. The two chords form approximately congruent triangles in systole and in diastole. This is true not only for an "ideal" ellipse but also for the more irregularly shaped ventricle. If Ud = K Dd and if Us = K Ds, where K is a constant and Ud and Us are the ultrasonic left ventricular axes during diastole and systole, respectively, then

$$EF = \frac{Ud^2 - Us^2}{Ud^2}.$$

A decreased ejection fraction occurs because of generalized or localized abnormalities, or both, in ventricular contraction. Echocardiography may have its greatest value, in that regard, in measuring generalized changes that can occur as a primary defect or in response to more localized disease. Echocardiography cannot detect mitral regurgitation directly, and in patients with this condition the ejection fraction tends to be high. Similarly, if the echocardiographic beam visualizes a localized area of hypokinesis in the septum or the posterior wall, a spuriously low ejection fraction will be calculated. Two studies, one recently reported[8] and one recently completed in our laboratory, support some of these theoretical considerations. Although more studies are needed, this method may allow the physician to compare ejection fractions in the same patient and among groups.

Compound-B ultrasonography: Another approach to this problem is compound-B ultrasonography.[9] The advantage of this method over conventional echocardiography is that both the longitudinal and orthogonal axes of the left ventricle can be measured in a complete study. Ventricular volume at end-diastole and at end-systole may be calculated by the area-length method of Sandler and Dodge.[10] However, in individual cases it may be difficult to outline the anatomic apex of the left ventricle, and the volume will be underestimated. The compound-B ultrasonic ejection fraction measures the relative change in cross-sectional area just as the conventional echocardiographic ejection fraction measures the relative decrease in minor axis. Besides being able to detect generalized abnormalities of ventricular contraction, compound-B ultrasonography can also indicate localized asynergic motion of the septum, posterior wall or apex.[11]

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LETTERS TO THE EDITOR

SURGICAL VS. MEDICAL THERAPY IN UNSTABLE ANGINA

The recently published preliminary report by Bertolasi et al.[1] of a prospective and randomized study of surgical versus medical therapy in unstable angina pectoris raises important questions that cast an element of doubt on the authors' conclusion that "... patients with the intermediate syndrome treated surgically appeared to have significantly reduced mortality."

In comparing medical with surgical therapy, it is important to define clearly the entire protocol of the medical therapy. The authors outlined only in very general terms medical treatment during the acute stage of the syndrome giving no details concerning long-term medical management except for a brief statement that: "... patients were evaluated at 4 month intervals." The data, as presented, thus appear to compare surgical treatment with, at best, variable medical therapy. Also, no information was provided for either group in regard to (1) length of stay in hospital, (2) frequency of follow-up visits and nature of medical treatment during the very important 3 or 4 months after onset of the intermediate syndrome, and (3) degree of physical activity permitted both groups during the same period.

In addition, the statement that "... those who survive surgery are in better clinical condition than the medically treated patients" is based on an interesting but arbitrary and potentially misleading index. No information was given concerning the circumstances of death, actual incidence of early and late myocardial infarction, episodes of acute coronary insufficiency and anginal status in the two groups at various times during the follow-up period.

Unless medically treated patients in such studies are subjected to specific protocols of treatment, comparison of the two groups gives rise to results that are of questionable validity, even in a preliminary report.

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Reference

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REPLY

Dr. Mizgala's questions allow us to update our preliminary report. The study, which ended in April 1973, included 146 patients with intermediate syndrome or progressive angina (cases with postinfarction angina are not considered here), 33 of whom were excluded for reasons mentioned in our article. The average hospital stay during the acute stage of the syndrome was 16.8 days; 100 percent of the included patients were followed up 13 to 47 months (average, 17.8). Each patient was studied every 4 months in order to obtain data, but of course was also examined as many times as required by his clinical course.

Of those patients with the intermediate syndrome, 28 were treated surgically; mortality rate and incidence of myocardial infarction were 10.7 percent and 14.2 percent, respectively. All deaths and infarctions occurred in the immediate postoperative period. Twenty-four patients were treated medically; mortality rate was 45.8 percent ($P < 0.005$) (the patients died, respectively, 2, 5, 7, 8 and 20 days after admission and in the 2nd, 3rd, 8th, 12th, 16th and 40th months of follow-up). Nine patients (37.5 percent, $P < 0.06$) had a myocardial infarction, six during the acute phase and three during the follow-up period.

Of those patients with progressive angina, 34 were treated surgically; mortality rate and rate of infarction were 8.8 percent and 11.7 percent, respectively. All deaths and infarctions occurred in the immediate postoperative period. Twenty-seven patients were treated medically; mortality rate was 7.4 percent ($P > 0.80$). The two deaths occurred, respectively, 2 days after admission and in the 12th month of follow-up; the rate of infarction was 7.4 percent ($P > 0.45$), one infarction occurring during the acute stage and the other during follow-up.

Deaths were attributed to ischemic heart disease (sudden death, myocardial infarction and cardiac failure) except for six deaths related to the surgical procedure (four occurring immediately after operation, one caused by renal failure and one due to sepsis). Two patients were excluded because their deaths were not related to heart disease or surgery (one due to gastric cancer and one to respiratory infection).

The medical treatment given has already been summarized in our paper, but we will comment briefly here on the anticoagulant therapy and the use of beta adrenergic blocking agents. Heparin was given in 25 percent of the cases, although our interest in that drug has lessened, especially since it has been postulated that thrombosis is frequently an epiphenomenon of the acute episode, particularly in cases of nontransmural necrosis without shock.[1] None of the patients received beta adrenergic blocking agents before coronary arteriography because of the increased risk to the patient. After the hemodynamic study propanolol or practolol was administered to 41 percent of the patients. These drugs were given when we suspected a "hyperkinetic state" or when they were not contraindicated by the left ventricular end-diastolic pressure or the left ventriculogram. We were not then aware of the report by Fischl et al.,[2] who obtained an excellent therapeutic response with doses of up to 400 mg of these drugs; however, in their group of patients, strictly defined according to criteria similar to ours, 14 were operated on with good results (one death), whereas the 9 who were treated medically had a mortality rate of 33 percent after 1 year, similar to the 37.5 percent rate recorded by us in the same period. These authors did not mention the complete medical protocol followed.

We followed no "specific protocol" for long-term treatment. We used isosorbide dinitrate, beta adrenergic blocking agents, diuretic agents and antiarrhythmic drugs for both medical and surgical groups. We did not use "metabolic" drugs or long-term anticoagulant agents. We evaluated the functional capacity of each patient through exercise testing.

Concerning our index, it is clearly the summary of the clinical results updated every 4 months. Figure 1, A and B,

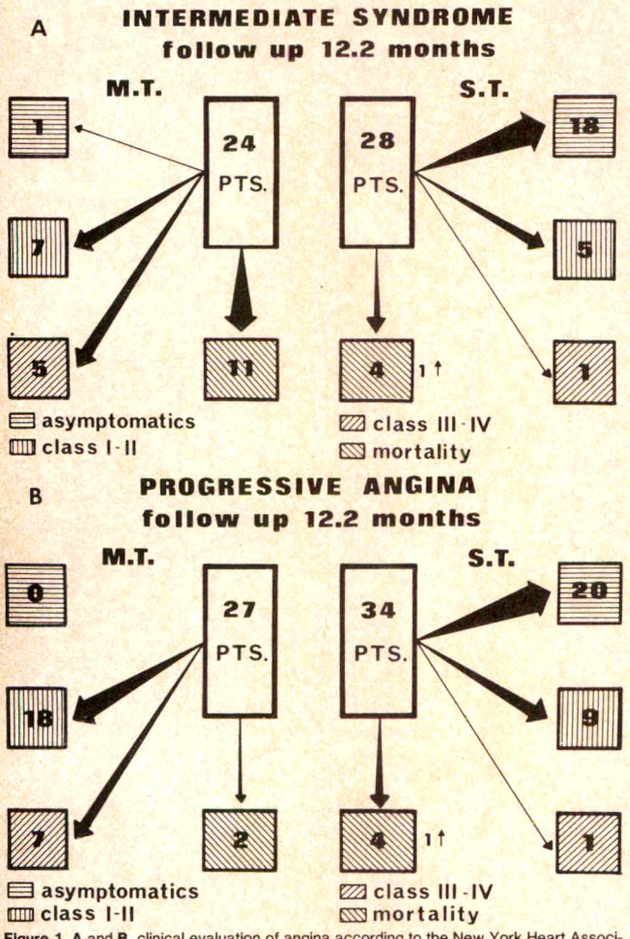

Figure 1. A and **B**, clinical evaluation of angina according to the New York Heart Association classification. One patient excluded (see text). M.T. = medical treatment. S.T. = surgical treatment; PTS = patients.

shows the results after 12 months of follow-up on the basis of symptoms of angina. These findings are supported by the identical results obtained in the more objective ergometric study.

Finally, it is possible that we did not place enough emphasis on the most important conclusion of our study. Among patients with unstable angina (excluding those with angina of recent onset and Prinzmetal's angina), there are two distinct groups: (1) those with the intermediate syndrome, and (2) those with progressive angina. Mortality rate and the incidence of myocardial infarction differ significantly in the two groups: 45.8 and 7.4 percent ($P < 0.002$) and 37.5 and 7.4 percent ($P < 0.01$), respectively. Theroux and Campeau[3] have reached similar conclusions.

The patients of Gazes et al.,[4] although not studied angiographically, were carefully selected and followed up during a 10 year period. These authors also identified two distinct courses for their patients and observed that after 1 year the mortality rate was 43 percent for the high risk group and 2 percent for the low risk group. Gazes et al. did not mention any specific treatment.

On the basis of the clinical pattern in patients with angina, we now identify several syndromes that have classically been known as preinfarction angina: (1) angina of recent onset with and without sudden loss of physical capacity; (2) Prinzmetal's angina; (3) intermediate syndrome; (4) progressive angina; (5) postacute myocardial infarction (angina within 1 month after an acute myocardial infarction); (6) acute persistent ischemia (this includes patients with the clinical findings of myocardial infarction [prolonged angina] without increased serum enzymes and with permanent modifications [more than 24 hours] in ventricular repolarization [T wave inversion]). We do not intend hereby to establish new classifications, which may increase confusion. Nevertheless, differences in the natural course of these patients suggest that it is wise to identify those in whom the therapeutic approach should probably differ.

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LIFE UNITS IN CORONARY ARTERY DISEASE

The conflicting opinions concerning the efficacy of surgery and the tendency to delineate more and more subgroups of patients with coronary disease make it obligatory for the responsible physician to judge as best he can into which subgroup his patient falls. In my opinion there are almost as many subsets as patients. There is much more to predicting a patient's natural history than knowledge of the anatomy of his coronary arteries. Even when the questionable random trials are concluded, it will still be the duty of the physician to take all knowledge of the patient—his lifestyle, his biochemistry and his response to treatment as well as the anatomy of his coronary arteries—into account and predict his natural history, using the published guidelines of authorities.

I suggest that the term "life units" be used as the currency of evaluation. Life units represent the number of years a person lives multiplied by the quality of life, which for practical purposes can be related to functional heart classification. Class IV quality of life is rated 1; class III, 2; class II, 3; and class I, 4. Thus, 2 years lived at the class I level is equivalent to

$$2 \times 4 = 8 \text{ life units}$$

If the predicted life units before surgery are compared with the life units after surgery, in time we will gain some idea of the significance of surgery for a particular patient.

The term life unit would enable us to cope, using one measure, with the various ways that surgery can improve a patient's condition, namely, reduction of pain, improvement in exercise tolerance, prevention of infarction and increase in life span. Unscientific and "soft" as it is, it is a useful working term for the clinician. It need not have the same significance for every patient or doctor, and that is a strength rather than a weakness. It is the individual that a clinician is evaluating, not a group of individuals.

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COMMENT

I share Dr. Tofler's view that there is, in essence, an infinite number of subsets of patients with coronary disease since

no two patients are identical. However, as physicians seeking to make the most rational judgments possible relative to major decisions affecting the life and health of our patients, we believe that it is necessary to cluster many of these subgroups on the basis of the best available information. Under essentially all circumstances, this judgment is based upon less than optimal information. However, this does not negate the value of meticulously performed studies of patients who can be clustered by one or several descriptors into reasonable population groups.

I am in complete sympathy with Tofler's desire to include the quality of life in any equation describing the outcome of alternative methods of treatment. His numerical quantitation is undoubtedly a severe oversimplification. Nevertheless, it has the attraction of simplicity and considerable validity presented in easily understandable quantitative units. Most physicians unconsciously apply some such thinking into their decision-making process. However, by expression in quantitative units, the relative merits of various treatments become more apparent. The hazard of such oversimplification is that greater emphasis may be placed upon the numerical product than is truly warranted. The application of such an equation to an analysis of patients is awaited with interest.

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ECHOCARDIOGRAM IN *d*-TRANSPOSITION OF GREAT VESSELS

Dillon et al.[1] recently proposed that "the echocardiographic finding of superimposition of the great vessels without intervening crista together with simultaneous recording of the semilunar valves is diagnostic for transposition of the great arteries." The validity of this new diagnostic criterion was later challenged by Glaser et al.,[2] but the evidence presented was refuted by Dillon.[3]

We agree with Dillon that the recordings presented by Glaser et al. are inconclusive, although we believe that the latter's objection is valid. This belief is based on echocardiographic recordings that we recently obtained from two cyanotic newborn infants who were later proved to have normally related great vessels by cardiac catheterization and angiocardiography.

Figure 1, from one of these infants, unequivocally shows both semilunar valves, recorded simultaneously, parallel to each other and without an intervening crista. It can be seen from this recording that the posterior aortic valve closes before the anterior pulmonary valve (arrows), as expected. The left atrium is seen behind the aortic valve. Another recording revealed normal continuity between the posterior aorta and the mitral valve. Similar findings were obtained in the second patient.

Although it is also our experience that the semilunar valves can be recorded simultaneously in most patients with transposition of the great arteries, we believe that the evidence presented here shows that this finding is not diagnostic, at least in the newborn. We have found useful the criteria proposed by Gramiak et al.[4] to determine the relation of the great arteries. In the two cases discussed here, use of this technique indicated normal relation of the great vessels.

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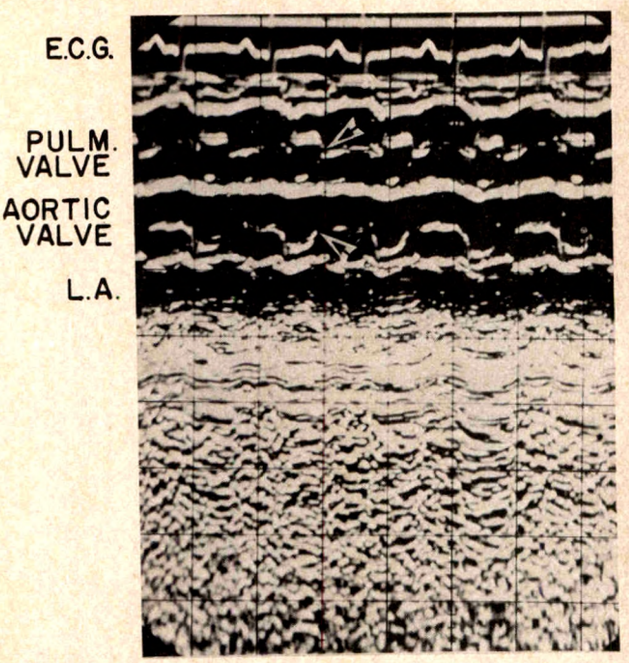

FIGURE 1. Echocardiogram from a 3 hour old term infant with cyanosis and normally related great vessels. E.C.G. = electrocardiogram; L.A. = left atrium; PULM. = pulmonary.

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A Cooperative Program of the American College of Cardiology and the National Library of Medicine

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BOOK REVIEWS

CLINICAL CARDIAC RADIOLOGY, by Keith Jefferson and Simon Rees. Toronto, Canada, Butterworths, 1973, 326 pages, $57.75

The authors present a clinically oriented book of interest to both cardiologists and radiologists. The material is based on their personal experience with radiologic findings in some 1,500 patients with various forms of cardiac disease, in whom physiologic and anatomic "answers" were available.

The book is divided into two parts: Part I, general radiology, presents an overall view of radiographic changes that occur in heart disease. Heart size and variations in size of the cardiac chambers, the great vessels and the systemic veins are first described. Included are comments on the position of the heart and its component parts and on calcification in the cardiovascular system. The next section is devoted to the lungs, including changes of pulmonary vascularity, effects of pulmonary hypertension, effects of pulmonary thromboembolism, and infarction. A brief third section describes other systems affected by heart disease, such as the bony thorax, changes occurring in some hereditary syndromes and relations between general systemic diseases and the heart. Part II, clinico-radiological approach to heart disease, systematically presents radiologic appearances and findings in various cardiac diseases, including congenital heart disease, valvular diseases and myocardial and pericardial diseases.

The book is written in clear language and is very well illustrated. The 377 figures (many containing several parts) consist largely of reproductions of radiographs, but there are also many anatomic drawings, diagrams and angiocardiographic reproductions. Angiograms are used only to illustrate specific points; contrast radiography, as such, is not discussed. In addition to illustrative material, there are many tables showing data and explaining certain clinical-radiographic relations and probabilities. A bibliography contains an alphabetically arranged list of approximately 300 cited articles.

In contrast to electrocardiography, which is covered by a veritable plethora of textbooks, few books have been devoted to cardiovascular radiography. This one is outstanding, primarily because of its correlation of clinical and physiologic data with radiographic findings. Written by radiologists who have a deep understanding of the pathophysiologic processes that occur in cardiac diseases, this book places radiography in its proper perspective: a technique that does not merely depict images of altered anatomic structures of the heart and related organs, but that also reflects changes produced by specific functional processes. The reader not only will receive information on the expected radiographic changes in various cardiac diseases and their role in diagnosis, but also will come away with a better comprehension of the underlying disease process. This volume is highly recommended to cardiologists and radiologists alike.

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President's Page: The College, Education and the Heart House Learning Center

The phrases "lifetime of learning," "prevention of obsolescence," "maintenance of professional competence" and other reminders of our professional obligation are heard daily by all of us. This emphasis on continued education is not new. Competent physicians have always recognized educational activities as an integral part of their professional life, the sole purpose of which has been to provide constantly improving, high quality patient care. However, because of the changes that are occurring so rapidly in medicine and cardiology, the educational aspects of professional life have reached crisis proportions. The potential for a very short "competency period" after completion of a training program is a source of frustration and, on occasion, panic. All too frequently, physicians are opting for early retirement, specialization in narrower areas of responsibility or, in other ways, are manifesting signs of failure to cope.

Widespread failure to cope with early obsolescence would be a tragedy for several reasons, not the least of which would be failure to discharge our responsibility to our patients. Failure on our part to provide guidelines and materials for continuing cardiologic education and failure to incorporate into the system methods for measuring achievement invites "outside" intervention. Regulatory controls imposed from without may be mediocre and therefore less acceptable than those we could devise for ourselves. In addition, provision needs to be made for a system that not only provides quality education for today but also investigates methods for continuing education of tomorrow in order that we avoid repetitive crises. Clearly, simple adherence to present educational methods will not suffice.

The recently formalized objectives for the Heart House Learning Center reflect the awareness of the College for the needs of today and the future and, as such, incorporate ongoing service functions as well as research in educational science. It seems appropriate to list these objectives:

1. To meet demonstrated and perceived educational needs of professional health personnel.
2. To construct a curriculum which will be responsive to changing needs, knowledge and teaching methods.
3. To establish a resource center for media and instructional techniques for intra- and extramural use.
4. To design improved methods of educational evaluation.
5. To establish improved teaching techniques.
6. To establish improved learning techniques.
7. To collaborate with other societies and institutions in accomplishing our educational goals.
8. To increase participation of health professionals in continuing medical education by assisting health professionals in designing learning experiences appropriate to their needs.
9. To provide for effective distribution of learning resources.
10. To monitor the total educational system with respect to cost-effectiveness and appropriate utilization.
11. To evaluate the degree to which the educational program has achieved the purpose of improving cardiovascular care.

Heart House is not just bricks and mortar. In addition to serving as the permanent headquarters for our College, it is an Institute for Research in Medical Education, a Learning Center and a Production Studio. The major goal is to provide a mechanism whereby the College members and others wishing to take advantage of the opportunity can be assured of being prepared for the delivery of quality cardiovascular care and assessment of that care which is surely forthcoming. Heart House is a continuous learning center. The need for "cramming" sessions should be minimal.

The College is committed to implementation of the above objectives.

Charles Fisch, MD, FACC
President
American College of Cardiology

Norms for Use in the Peer Review of Selected In-Hospital Cardiovascular Diagnoses

Developed by the American College of Cardiology
Bethesda, Maryland
April 1, 1975*

FOREWORD

In 1974 the American College of Cardiology published (*American Journal of Cardiology* 33:697–709, 1974) norms for use in peer review of the quality of cardiovascular practice which were subject to periodic review. The American Medical Association (AMA) has since contracted with the Department of Health, Education, and Welfare (DHEW) to generate norms for use in PSRO. The present Norms represent a modification of the previous Norms to conform to a common format employed by all medical specialties. Along with the criteria developed by other medical specialties, these criteria will be submitted to DHEW for approval and dissemination to regional PSRO's. Regional PSRO's may accept these criteria for peer review, or they may generate their own local criteria.

According to the format developed by the AMA, Items I and II will serve for Concurrent Review; Items V and VI for Retrospective Review; Items III and IV, though intended primarily for Retrospective Review, may also serve for Concurrent Review.

The criteria to be published by DHEW will include specific instructions for their application. For example, it is assumed that all deaths will be reviewed; consequently, Item V (Discharge Status) makes no reference to death as a criterion for review. It should also be emphasized that the criteria were written to be as inclusive and straightforward as possible for use by paramedical clerks.

The official position of the American College of Cardiology toward PSRO is explained in the original publication.

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* *Members of ACC Cardiovascular Norms Committee are R. Joe Noble, MD, FACC, Chairman; Maxwell G. Berry, MD, FACC; Louis Gillespie, Jr., MD, FACC; Brendan Phibbs, MD, FACC; Arthur Selzer, MD, FACC; and Sylvan L. Weinberg, MD, FACC.*

Address for reprints: Mr. William D. Nelligan, Executive Director, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

DIAGNOSIS/PROBLEM:
CONGESTIVE HEART FAILURE
427.0 (Code Number)

I. *Justification for admission*
- A. Suspicion of or diagnosis of pulmonary edema
- B. Newly diagnosed CHF, to establish response to therapy
- C. Unresponsive to outpatient management (i.e., persistent or recurrent symptoms of dyspnea, weakness, edema)
- D. Diagnostic admission; i.e., to establish etiology, functional significance of lesion, anatomic or physiologic derangement (e.g., cardiac catheterization)

II. *Length of stay*
- A. Initial length of stay assignment for primary diagnosis or problem (numerical determinations to be established locally based on statistical norms)
- B. Extended length of stay assignment (numerical determinations to be established based on the individual patient's condition at the end of the initial length of stay period)
  1. Reasons for extending the initial length of stay
     - a. Persistent symptomatology; i.e., refractory heart failure
     - b. Pulmonary embolization
     - c. Renal insufficiency and/or electrolyte imbalance
     - d. Arrhythmia
     - e. Myocardial infarction

III. *Validation of:*
- A. Diagnosis
  1. Positive chest X-ray findings of pulmonary congestion; or
  2. Positive physical findings of gallop rhythm, or venous hypertension or edema or enlarged heart; or
  3. Improvement following digitalis or diuretics
- B. Reasons for admission
  1. Serious clinical disability (dyspnea, edema, weakness), I-C
  2. Invasive procedures based on suspicion of surgically remediable lesion, I-D

IV. *Critical diagnostic and therapeutic services*
- A. Electrocardiogram (100%)
- B. Chest X-ray (100%)
- C. Serum electrolytes and blood urea nitrogen or creatinine (100%)

V. *Discharge status*
- A. Improvement in symptoms (III B-1); and signs (III A-2)
- B. Documented plan of follow-up

VI. *Complications*
- A. Primary disease and treatment-specific complications
  1. Rising blood urea nitrogen
  2. New arrhythmia, interpreted as consistent with digitalis intoxication
  3. Digitalis toxicity (digoxin level >4 ng/ml; digitoxin level >40 ng/ml)
- B. Nonspecific indicators
  1. Surgery

DIAGNOSIS/PROBLEM: HYPERTENSION
(INCLUDE ACCELERATED, ENCEPHALOPATHY)
401.0 (Code Number)

I. *Justification for admission*
- A. Diastolic blood pressure in excess of 115 mm Hg
- B. Failure to respond to antihypertensive therapy
- C. Neurologic or sensorium abnormalities
- D. Suspicion of secondary cause of hypertension (e.g., renal disease, renal vasculature abnormality, adrenal disease)
- E. Uncontrolled congestive heart failure (see Congestive heart failure), renal failure (rising blood urea nitrogen)

II. *Length of stay*
- A. Initial length of stay assignment for primary diagnosis or problem (numerical determinations to be established locally based on statistical norms)
- B. Extended length of stay assignment (numerical determinations to be established based on the individual patient's condition at the end of the initial length of stay period)
  1. Reasons for extending the initial length of stay
     - a. Secondary cause of hypertension discovered (e.g., renal disease, renal vasculature abnormality, adrenal disease)
     - b. Unresponsive to initial antihypertensive therapy
     - c. Neurologic abnormalities
     - d. Congestive heart failure
     - e. Renal failure (rising blood urea nitrogen or creatinine)

III. *Validation of:*
- A. Diagnosis
  1. Diastolic blood pressure in excess of 90 mm Hg
- B. Reasons for admission
  1. Historical documentation of I-B

IV. *Critical diagnostic and therapeutic services*
- A. Blood pressure recorded daily, as a minimum (100%)
- B. Blood urea nitrogen or creatinine (100%)
- C. Electrocardiogram (100%)
- D. Fundoscopy (100%)
- E. Chest X-ray (100%)

V. *Discharge status*
- A. Anti-hypertensive therapy (e.g., salt restriction, antihypertensive medication)
- B. Documented plan of follow-up
- C. Resolution of reason for admission

VI. *Complications*
- A. Primary disease and treatment-specific complications
  1. None
- B. Nonspecific indicators
  1. Surgery

DIAGNOSIS/PROBLEM:
ARTERIOSCLEROTIC HEART DISEASE
(INCLUDE ANGINA PECTORIS AND "CHEST PAIN")
412.0 (Code Number)

I. *Justification for admission*

A. Suspicion of unstable angina pectoris, including new angina pectoris
B. Scheduled for coronary cineangiography

II. *Length of stay*
A. Initial length of stay assignment for primary diagnosis or problem (numerical determinations to be established locally based on statistical norms)
B. Extended length of stay assignment (numerical determinations to be established based on the individual patient's condition at the end of the initial length of stay period)
1. Reasons for extending the initial length of stay
a. Persistent, recurrent angina pectoris
b. Additional diagnostic evaluation (coronary cineangiography)
c. Complications of diagnostic procedures (e.g., arterial occlusion, bleeding)
d. Myocardial infarction

III. *Validation of:*
A. Diagnosis
1. History is sufficient;or
2. Electrocardiographic confirmation of myocardial infarction; or
3. Stress electrocardiographic test positive or resting electrocardiogram during spontaneous angina positive; or
4. Coronary cineangiographic confirmation
B. Reasons for admission
1. Suspicion of angina or positive electrocardiographic findings of ischemia (rest or exercise), I-B

IV. *Critical diagnostic and therapeutic services*
A. Electrocardiogram (100%)
B. Chest X-ray (100%)

V. *Discharge status*
A. Patient's condition clinically stable or improving
B. Documented plan of follow-up

VI. *Complications*
A. Primary disease and treatment-specific complications
1. Complications of coronary cineangiography and catheterization (e.g., arterial occlusion, bleeding)
B. Nonspecific indicators
1. Surgery

DIAGNOSIS/PROBLEM:
MYOCARDIAL INFARCTION, ACUTE
410.0 (Code Number)

I. *Justification for admission*
A. Suspicion of or diagnosis of acute myocardial infarction
B. Suspicion of unstable angina pectoris

II. *Length of stay*
A. Initial length of stay assignment for primary diagnosis or problem (numerical determinations to be established locally based on statistical norms)
B. Extended length of stay assignment (numerical determinations to be established based on the individual patient's condition at the end of the initial length of stay period)
1. Reasons for extending the initial length of stay
a. Persistent arrhythmia
b. Congestive heart failure or shock
c. Aneurysm, mitral regurgitation, ventricular septal perforation
d. Recurrent pain (including pericarditis)
e. Pulmonary embolization
f. Coronary bypass surgery

III. *Validation of:*
A. Diagnosis
1. Electrocardiographic interpretation of acute myocardial infarction; or
2. Elevation in serum cardiac enzymes (creatine phosphokinase, glutamic oxaloacetic transaminase, lactic dehydrogenase, etc); or
3. Classic history and hospital course even in absence of 1 and 2 (e.g., chest pain, interpreted as consistent with myocardial infarction. No specific modifiers required)
B. Reasons for admission
1. No entry necessary

IV. *Critical diagnostic and therapeutic services*
A. Monitoring of cardiac rhythm (100%)
B. Intravenous infusion line maintained (100%)
C. Coronary care unit, if available (100%)
D. Serial electrocardiograms (100%)
E. Serial cardiac enzymes (100%)

V. *Discharge status*
A. Pain-free
B. Documented plan of follow-up

VI. *Complications*
A. Primary disease and treatment-specific complications
1. Arrhythmia interpreted as consistent with digitalis intoxication
B. Nonspecific indicators
1. None

DIAGNOSIS/PROBLEM: ATRIAL FIBRILLATION (CRITERIA APPLICABLE TO OTHER ARRHYTHMIAS) 427.4 (Code Number)

I. *Justification for admission*
A. Newly diagnosed
B. Rapid rate requiring prompt slowing (or slow rate, with other arrhythmia)
C. Failure to respond to ambulatory antiarrhythmic therapy
D. Symptoms of chest pain, syncope, dyspnea, or embolization

II. *Length of stay*
A. Initial length of stay assignment for primary diagnosis or problem (numerical determinations to be established locally based on statistical norms)
B. Extended length of stay assignment (numerical determinations to be established based on the individual patient's condition at the end of the initial length of stay period)
1. Reasons for extending the initial length of stay
a. Chest pain (angina → infarction)
b. Congestive failure or shock
c. Unresponsive to initial therapy

d. Serious ventricular arrhythmias
e. Pacemaker therapy

III. *Validation of:*
A. Diagnosis
1. Electrocardiographic documentation of rhythm disturbance
B. Reasons for admission
1. No entry necessary

IV. *Critical diagnostic and therapeutic services*
A. Electrocardiogram (100%)
B. Chest X-ray (100%)

V. *Discharge status*
A. Heart rate controlled within normal range
B. Free of chest pain, syncope, dyspnea

VI. *Complications*
A. Primary disease and treatment-specific complications
1. New rhythm disturbance interpreted as consistent with drug intoxication
B. Nonspecific indicators
1. None

DIAGNOSIS/PROBLEM:
VALVULAR HEART DISEASE
424.0 (Code Number)

I. *Justification for admission*
A. Scheduled for cardiac catheterization
B. Valvular heart disease complicated by heart failure, chest pain, syncope, hemoptysis or emboli
C. Suspicion of or diagnosis of aortic stenosis

II. *Length of stay*
A. Initial length of stay assignment for primary diagnosis or problem (numerical determinations to be established locally based on statistical norms)
B. Extended length of stay assignment (numerical determinations to be established based on the individual patient's condition at the end of the initial length of stay period)
1. Reasons for extending the initial length of stay
a. Arrhythmias
b. Bacterial endocarditis
c. Congestive heart failure
d. Thromboembolism
e. Hemodynamically significant valvular lesion warranting surgery

III. *Validation of:*
A. Diagnosis: Documentation of any of the following:
1. Characteristic physical findings
2. Cardiac catheterization confirmation
3. Compatible electrocardiographic interpretation
4. Compatible radiographic interpretation
5. Compatible echocardiographic interpretation
B. Reasons for admission
1. Presence of valvular heart disease complicated (e.g., congestive heart failure, chest pain, syncope, hemoptysis, or emboli) I-A,B

IV. *Critical diagnostic and therapeutic services*
A. Electrocardiogram (100%)
B. Chest X-ray (100%)

V. *Discharge status*
A. Anatomic diagnosis established
B. Patient's condition clinically stable or improving
C. Documented plan of follow-up

VI. *Complications*
A. Primary disease and treatment-specific complications
1. Complications of catheterization (eg, arterial occlusion, bleeding)
2. Bacterial endocarditis developing during hospitalization
B. Nonspecific indicators
1. Persistent fever

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AMERICAN COLLEGE OF CARDIOLOGY

New Orleans, Louisiana **February 23–26, 1976**

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  Entries must be postmarked no later than September 22, 1975
- **Technical Exhibits**
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  Deadline for requests for space: October 13, 1975
- **Young Investigators' Awards Competition**
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For application forms, write Patrick A. Ziarnik, Director, Annual Scientific Session Department, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

1975

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

AUG. 23–25 — **Tutorials in the Tetons (Cardiac Emergencies).** Robert S. Eliot, FACC, director and Robert J. Davis, FACC, Alan D. Forker, FACC, Vincent F. Miscia, FACC and Gerald L. Wolf, co-directors. Grand Teton National Park, Moran, Wyo.

SEPT. 8–9 — **Stress Electrocardiography.** Borys Surawicz, FACC, and Paul L. McHenry, FACC, directors. University of Kentucky Medical Center, Lexington, Ky.

SEPT. 22–26 — **Core Curriculum: Mechanisms and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC, director and Albert N. Brest, FACC, co-director. The Lankenau Hospital, Philadelphia, Pa.

SEPT. 30–OCT. 2 — **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya and James C. Dillon, FACC, co-directors. Indianapolis Hilton Hotel, Indianapolis, Ind.

OCT. 6–15 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. Crown Center Hotel, Kansas City, Mo.

OCT. 8–9 — **Louis N. Katz Symposium—Coronary Artery Disease 1975: Dilemma, Dialogue and Decision.** Sylvan Weinberg, FACC, Leonard S. Dreifus, FACC, Herman Hellerstein, FACC and Herman Uhley, FACC, directors. Good Samaritan Hospital, Dayton, Ohio

OCT. 9–11 — **New Techniques and Concepts in Cardiology: Pathogenesis, Diagnosis and Treatment of Coronary Atherosclerosis.** Stephen E. Epstein, FACC, director. Washington Hilton Hotel, Washington, D.C.

OCT. 14–16 — **Ischemic Heart Disease: Current Concepts.** William J. Grace, FACC, director and Richard J. Kennedy, FACC and James T. Mazzara, FACC, co-directors. St. Vincent's Hospital and Medical Center of New York, New York, N.Y.

NOV. 6–8 — **Core Curriculum: Phonocardiography and Pulse Recording—Workshop.** Morton E. Tavel, FACC, director. The Methodist Hospital Graduate Medical Center, Indianapolis, Ind.

NOV. 12–14 — **Core Curriculum: Echocardiography, Phonocardiography and Pulse Tracings—A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

DEC. 7–9 — **Advances in Heart Disease 1976.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, Calif.

DEC. 7–10 — **Structure—Function Correlations in Cardiovascular Disease.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, Va.

DEC. 10 — **Colloquia in Cardiology—Number 8: Sudden Death and Myocardial Infarction: New Observations.** Robert W. Oblath, FACC, Ronald Danzig, FACC and Sam H. Stone, FACC, directors. Ambassador Hotel, Los Angeles, Calif.

DEC. 12–14 — **The Dwight E. Harken Symposium: Advances in the Prophylaxis and Therapy of Cardiovascular Disease.** Henry I. Russek, FACC, director. Americana Hotel, New York, N.Y.

1976

JAN. 11–13 — **Future Directions in the Management of Cardiac Disease.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC and James S. Forrester, co-directors. Snowmass-at-Aspen, Aspen, Colo.

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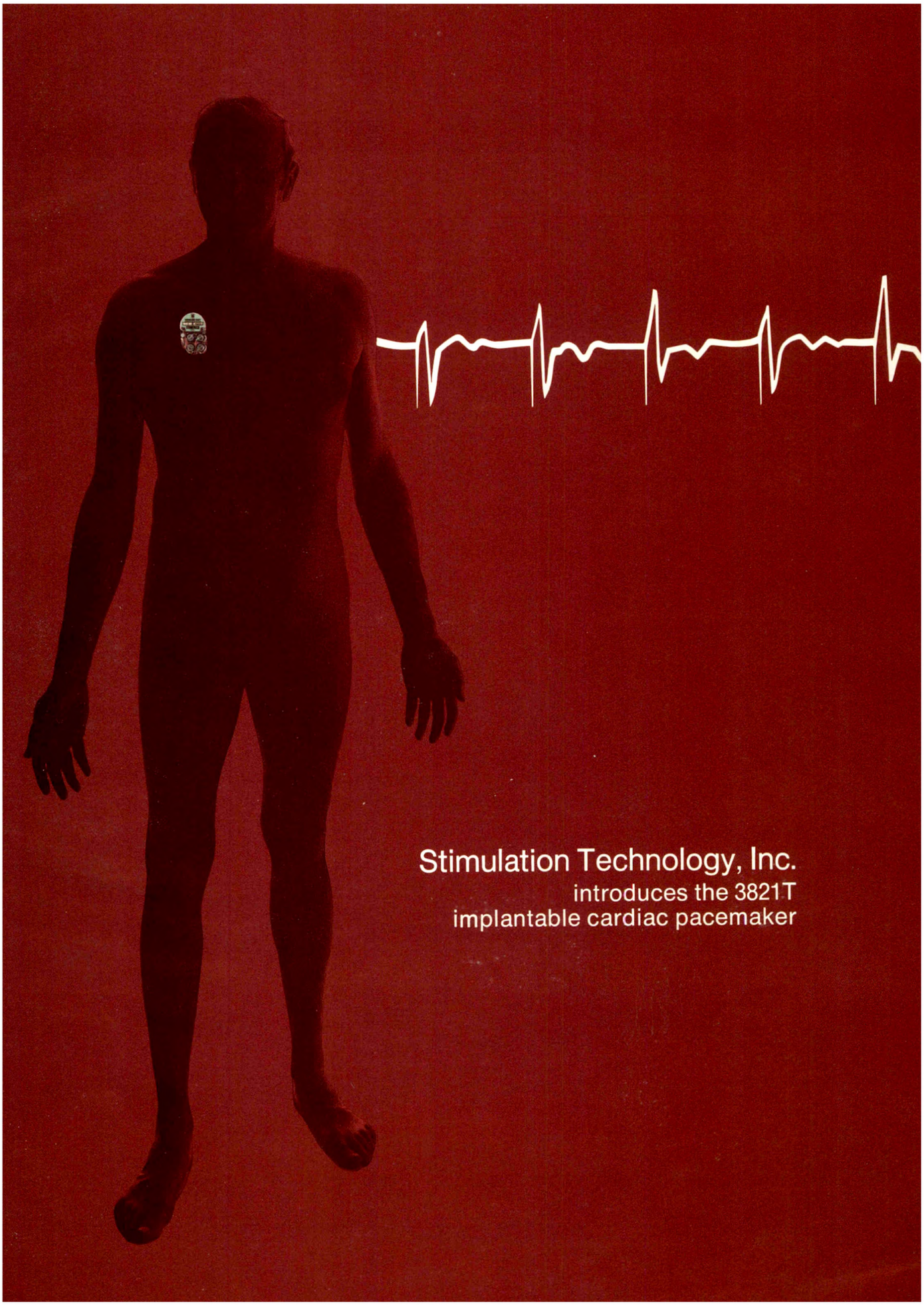

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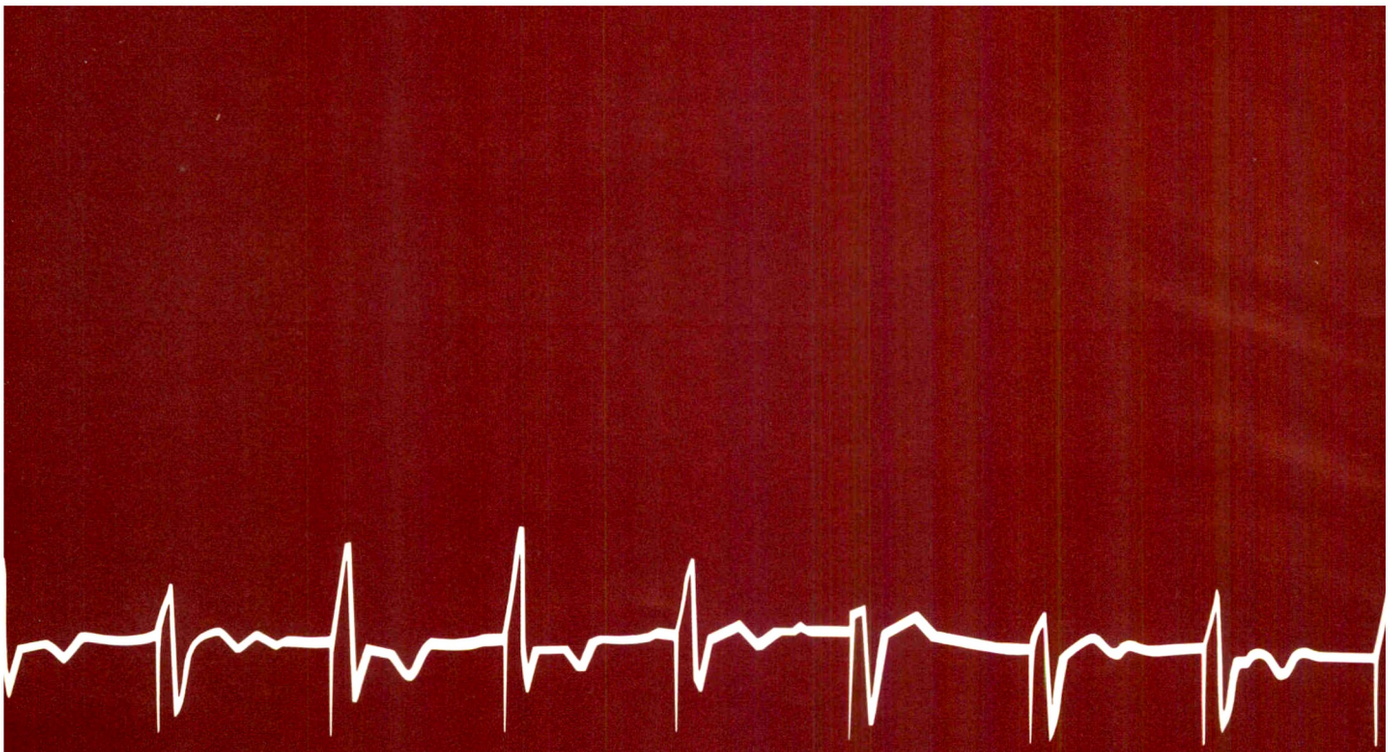

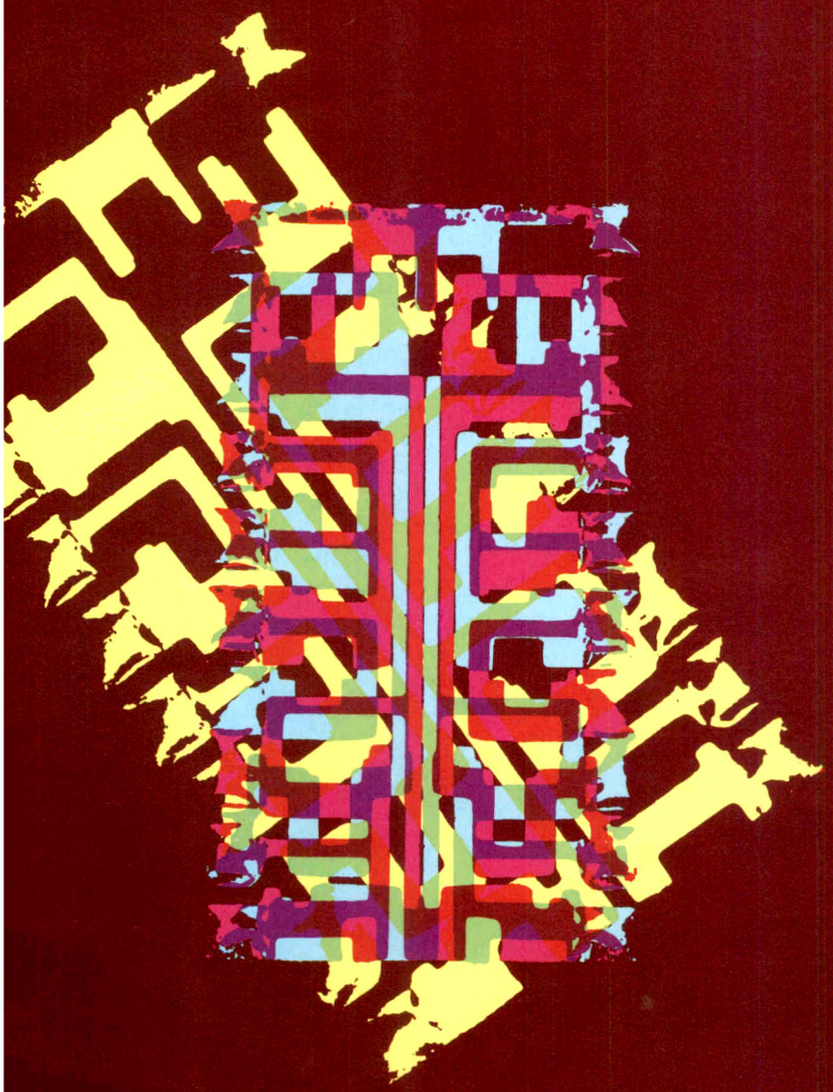

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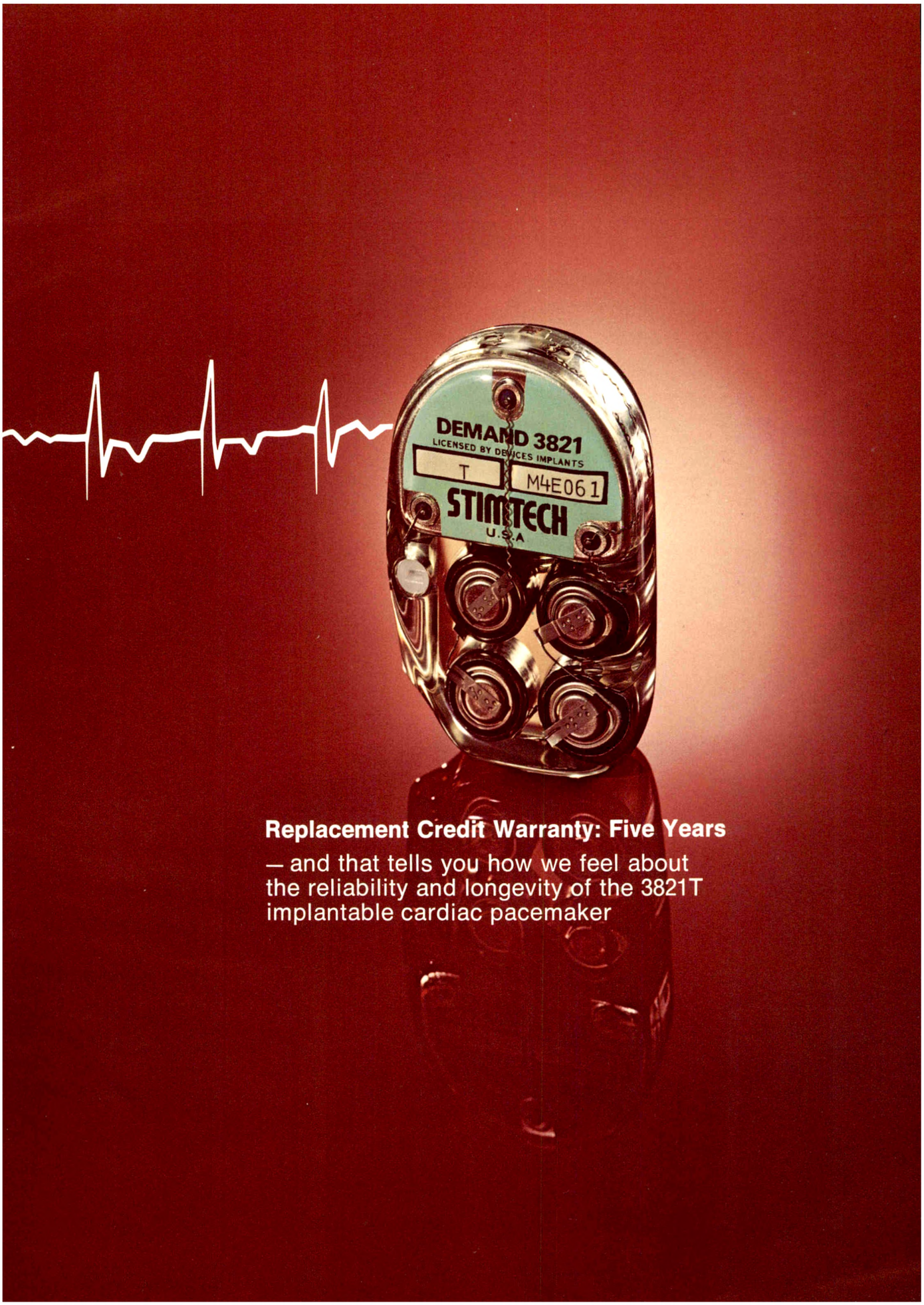

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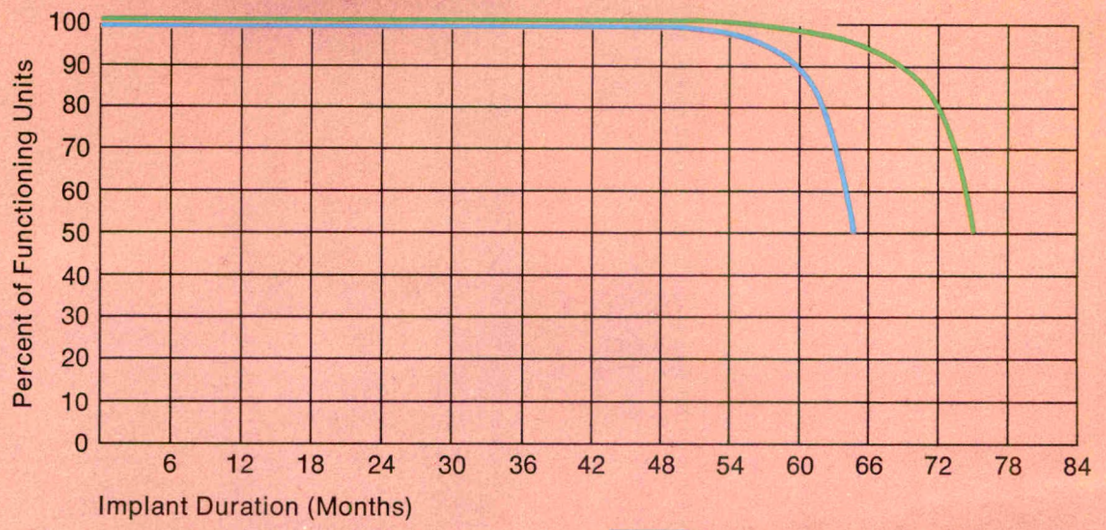

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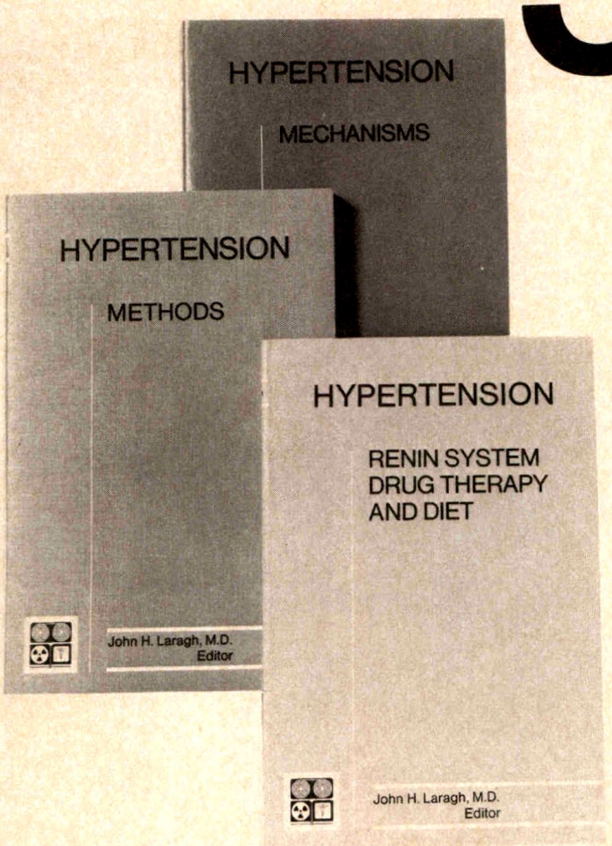

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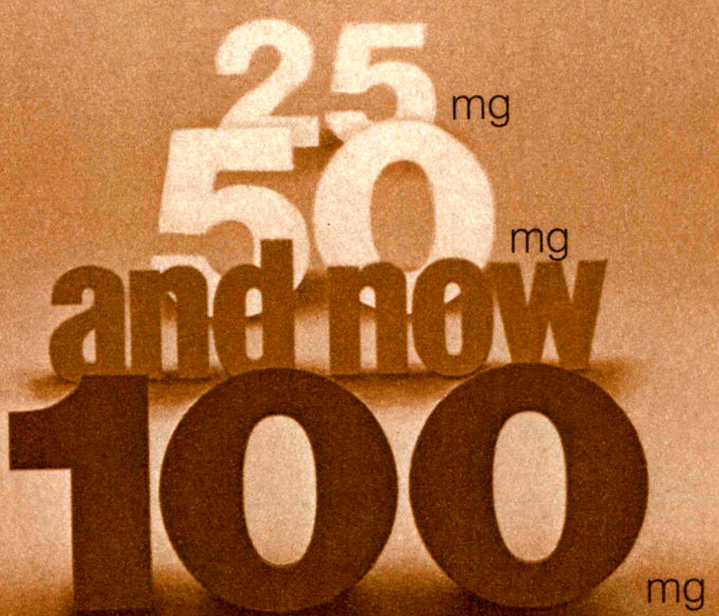

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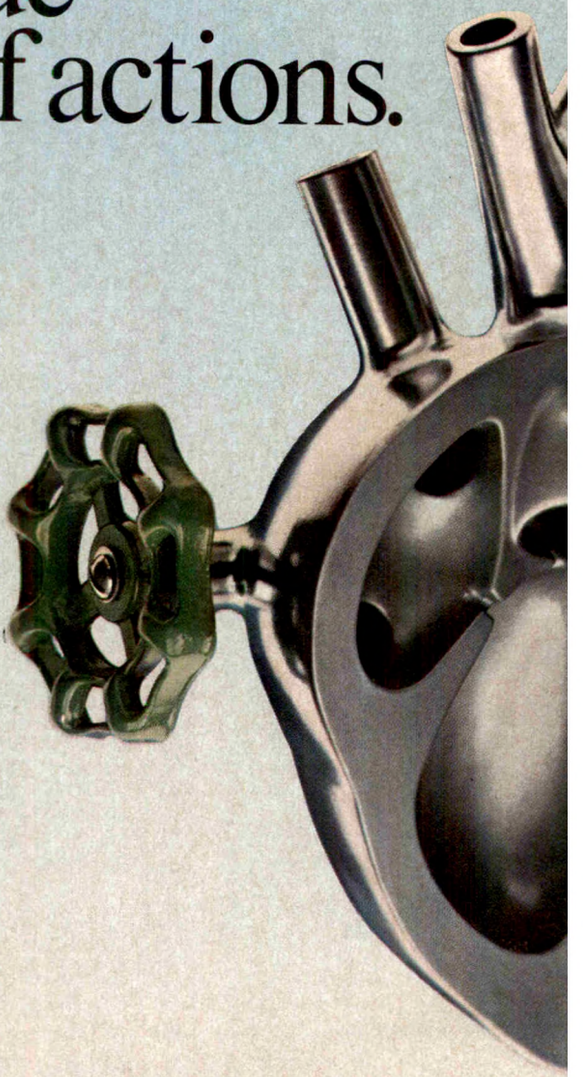

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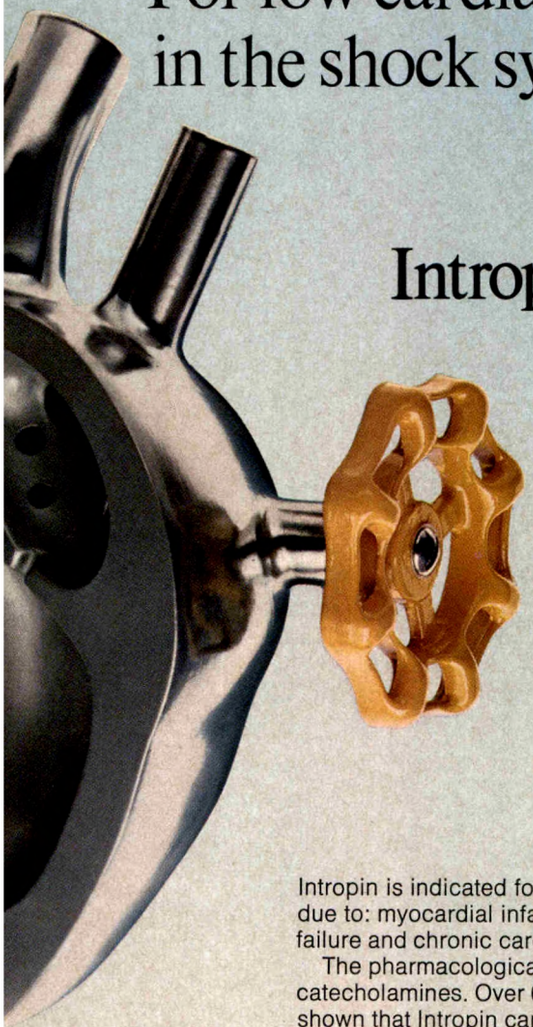

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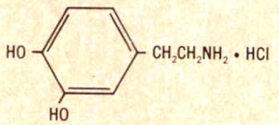

$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs—Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output—Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension—Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do NOT add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy—Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children—The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Although in clinical trials inadvertent subcutaneous infiltration did not produce any evidence of necrosis, the usual precautions should be taken to avoid extravasation.

Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Close monitoring of the following indices—urine flow, cardiac output and blood pressure—during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution—Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration—INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter.

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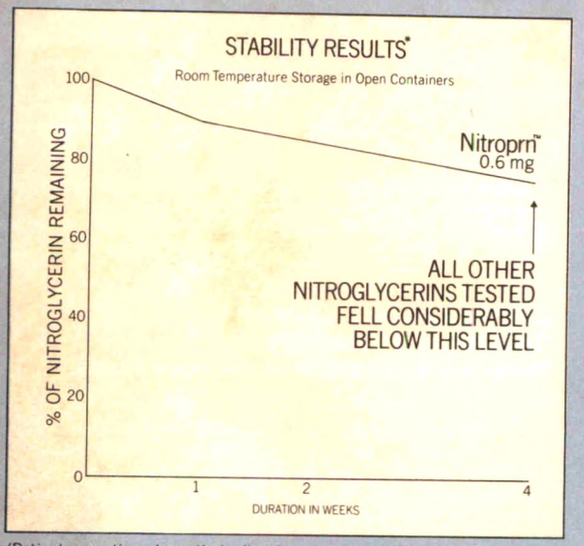

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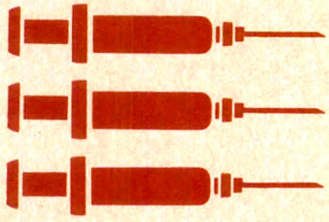
I.V. Administration Guidelines for Premature Ventricular Contractions and Tachycardia

1. Preparation of drug: Dilute before I.V. use.
2. Usual dosage range: 200-1000 mg.
3. Infusion rate: Not to exceed 25-50 mg. per minute. Total I.V. dose not to exceed 1000 mg.
4. Precautionary measures:
   a. Keep patient in supine position.
   b. Monitor electrocardiographically and discontinue if myocardial toxicity is evidenced.
   c. Measure blood pressure almost continuously and temporarily discontinue infusion if blood pressure falls more than 15 mm. Hg.

When therapeutic blood levels are required quickly, I.V. Injections

100 mg. every 5 minutes until arrhythmia suppressed (up to a maximum dose of 1 gram).



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I.V. Infusion

2-6 mg. per minute[1].
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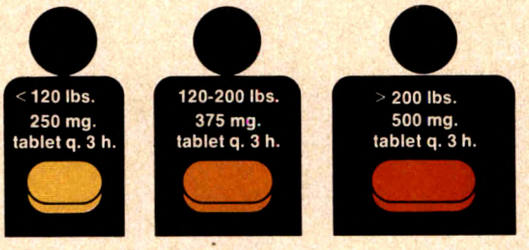
1. Wyman MG, Hammersmith L: Am J Cardiol 33:661-667, 1974
2. Bigger JT, Jr., Giardina EV: MCV Quart 9 (1): 65-76, 1973

Terminate I.V. infusion *4 hours before* oral regimen begun.

Oral Administration Guidelines to Provide 50 mg./kg./day* for Ventricular Arrhythmias

Ventricular Tachycardia
(give priming dose of 1 g. if patient has not received prior infusion)

Premature Ventricular Contractions



*This dosage schedule is for use as a guide for treating the average patient, but all patients must be considered on an individual basis.

Pronestyl®
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through the entire therapeutic course

See next page for brief summary.

PRONESTYL® TABLETS
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The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

Pronestyl Tablets (Procainamide Hydrochloride Tablets) are veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

Administration: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

How Supplied: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100.

PRONESTYL® INJECTION
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Description: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is a sterile aqueous solution providing 100 mg. or 500 mg. procainamide hydrochloride per ml. The 100 mg./ml. potency contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives. The 500 mg./ml. potency contains 0.1% methylparaben and not more than 0.2% sodium bisulfite as preservatives.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. *Intravenous use should be limited to extreme emergencies,* **the drug should be administered as a dilute infusion,** and the patient should be monitored electrocardiographically. The intravenous dose should not exceed 1 gram. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions.

How Supplied: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is available in 10 ml. vials providing 100 mg./ml. and in 2 ml. vials providing 500 mg./ml. © 1974 E. R. SQUIBB & SONS, INC. 444-009

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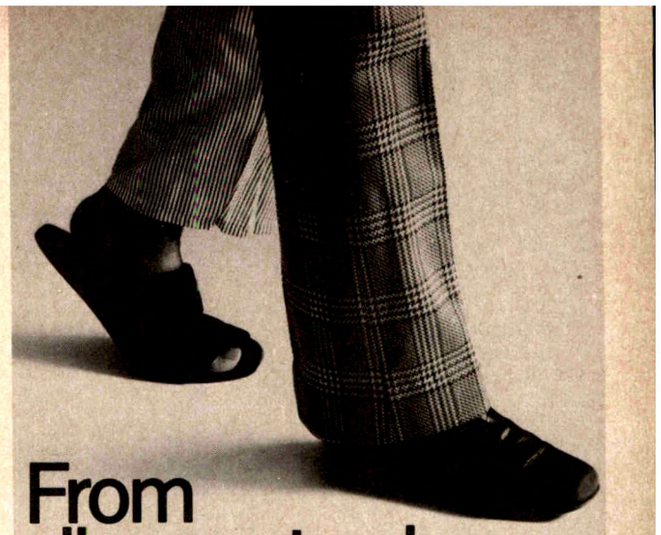

From slippers to shoes

chewable 10 mg

Cardilate®

(erythrityl tetranitrate)

increases exercise tolerance for your angina patient

Rx: chewable tablets 10 mg tid or qid (prn)

An effect appears in approximately 5 minutes —total duration of effect up to 4 hours.

For use in the prophylaxis and long-term treatment of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris.

Precautions: As with other effective nitrites, some fall in blood pressure may occur with large doses. Caution should be observed in administering the drug to patients with a history of recent cerebral hemorrhage, because of the vasodilation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

Side Effects: No serious side effects have been reported. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics.

Mild gastrointestinal disturbances occur occasionally with larger doses and may be controlled by reducing the dose temporarily.

Complete literature available on request from Professional Services Dept. PML.

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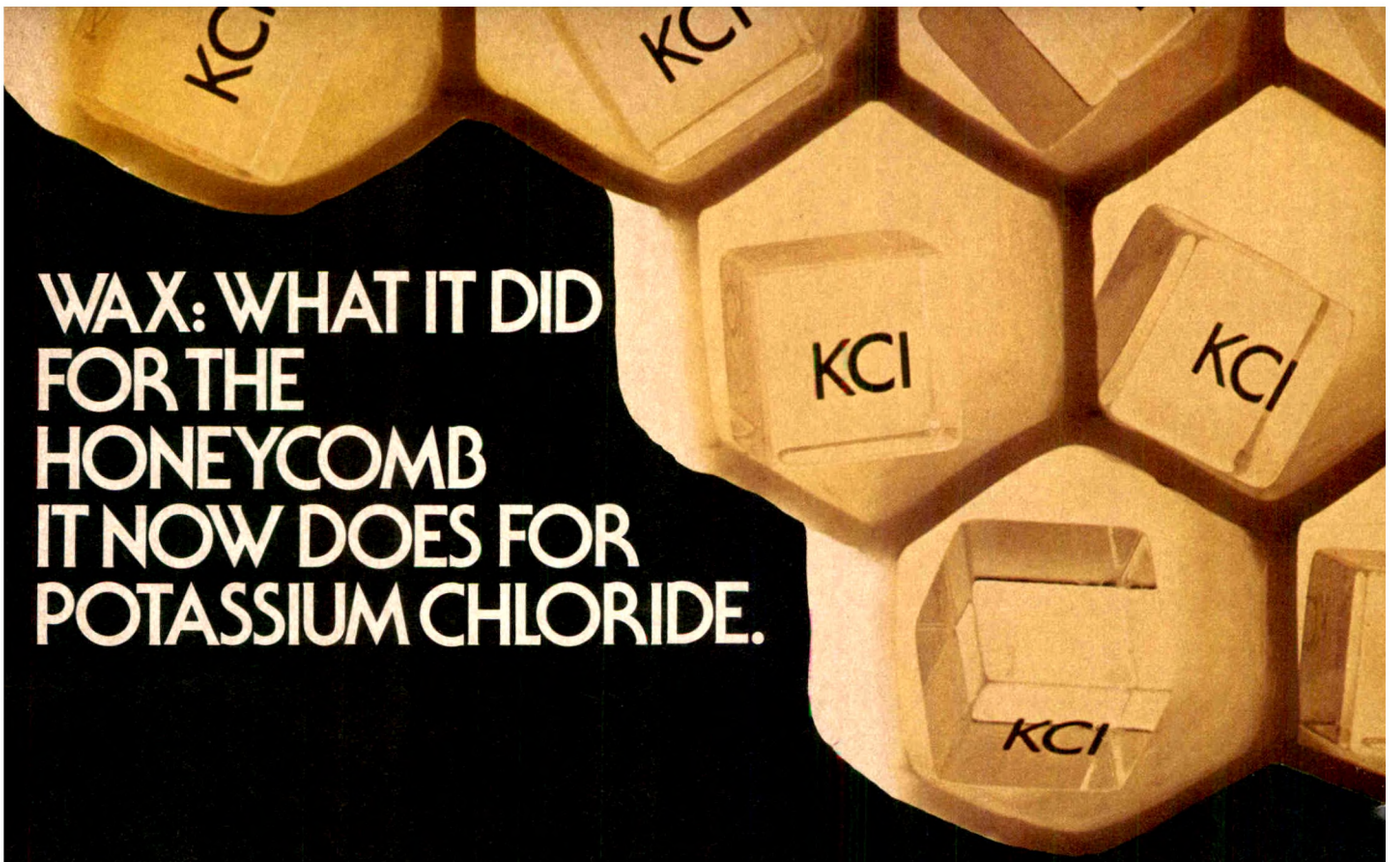

WAX: WHAT IT DID FOR THE HONEYCOMB IT NOW DOES FOR POTASSIUM CHLORIDE.

WARREN-TEED® ANNOUNCES

NEW KAON-CL TABS™

(potassium chloride)

CONTROLLED RELEASE TABLETS

– Potassium chloride imbedded in a wax matrix to provide controlled release, thus minimizing possible high local concentration of potassium ion near the bowel wall. The newest idea in potassium chloride supplements is as old as the beehive. Wax... provides an effective vehicle to imbed KCl crystals for a controlled rate of release

New Kaon-CL Tabs™
(potassium chloride)

prolong the release of KCl to minimize the likelihood of producing high localized concentrations of potassium within the G.I. tract...

- protect your patient from the risk of hypokalemia or digitalis intoxication due to potassium depletion that diet alone cannot correct...
- promote adherence to medication schedule by relieving the patient of the inconvenience of liquids...

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- because there's no palatability problem
- because there's no dilution problem
- because tablets are physically easier to carry—and to take—than liquids... an especially welcome advantage away from home—encouraging adherence to the prescribed regimen

The controlled release KCl Tablet that protects your patients on diuretics or digitalis

- against hypokalemia due to potassium depletion that cannot be adequately replaced by diet alone
- against the inconvenience of—and often confusion over—dilution of liquid supplements
- from taste-fatigue associated with liquids

Dosage: Prophylactic: 20 mEq. daily (1 tab T.I.D.)
Therapeutic: 40-100 mEq. daily
See following page for brief summary.

WARREN-TEED
PHARMACEUTICALS INCORPORATED
SUBSIDIARY OF ROHM AND HAAS COMPANY
COLUMBUS, OHIO 43215

Warren-Teed®
KAON-CL TABS™
(Potassium Chloride)
CONTROLLED RELEASE TABLETS

Description: Kaon-CL Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg. potassium chloride (equivalent to 6.67 mEq. potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: Kaon-CL Tabs is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. Kaon-CL Tabs is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

Warnings: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-CL Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric coated potassium chloride tablets (40-50 per 100,000 patient-years), a few cases associated with wax-matrix tablets have been reported. These data are from foreign marketing experience. Kaon-CL Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia, in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Dosage and Administration: Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq. per day for the prevention of hypokalemia to 40-100 mEq. per day or more for the treatment of potassium depletion.

One Kaon-CL Tabs three times daily provides 20 mEq. of potassium chloride. Two Kaon-CL Tabs three times daily provides 40 mEq. of potassium chloride.

Caution: Federal law prohibits dispensing without prescription.

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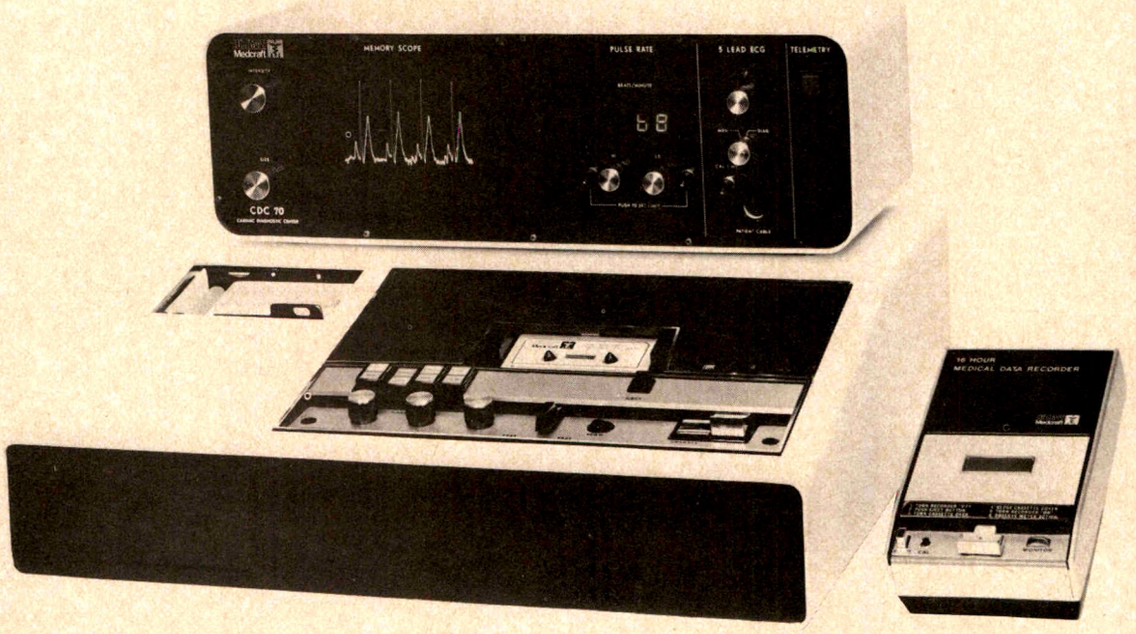

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As with sublingual ISDN:
acts in 2 minutes for therapeutic use...
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In addition:
chewing action helps distribute nitrate over a larger mucosal area.

SUMMARY OF
PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS
Division of ICI United States Inc.
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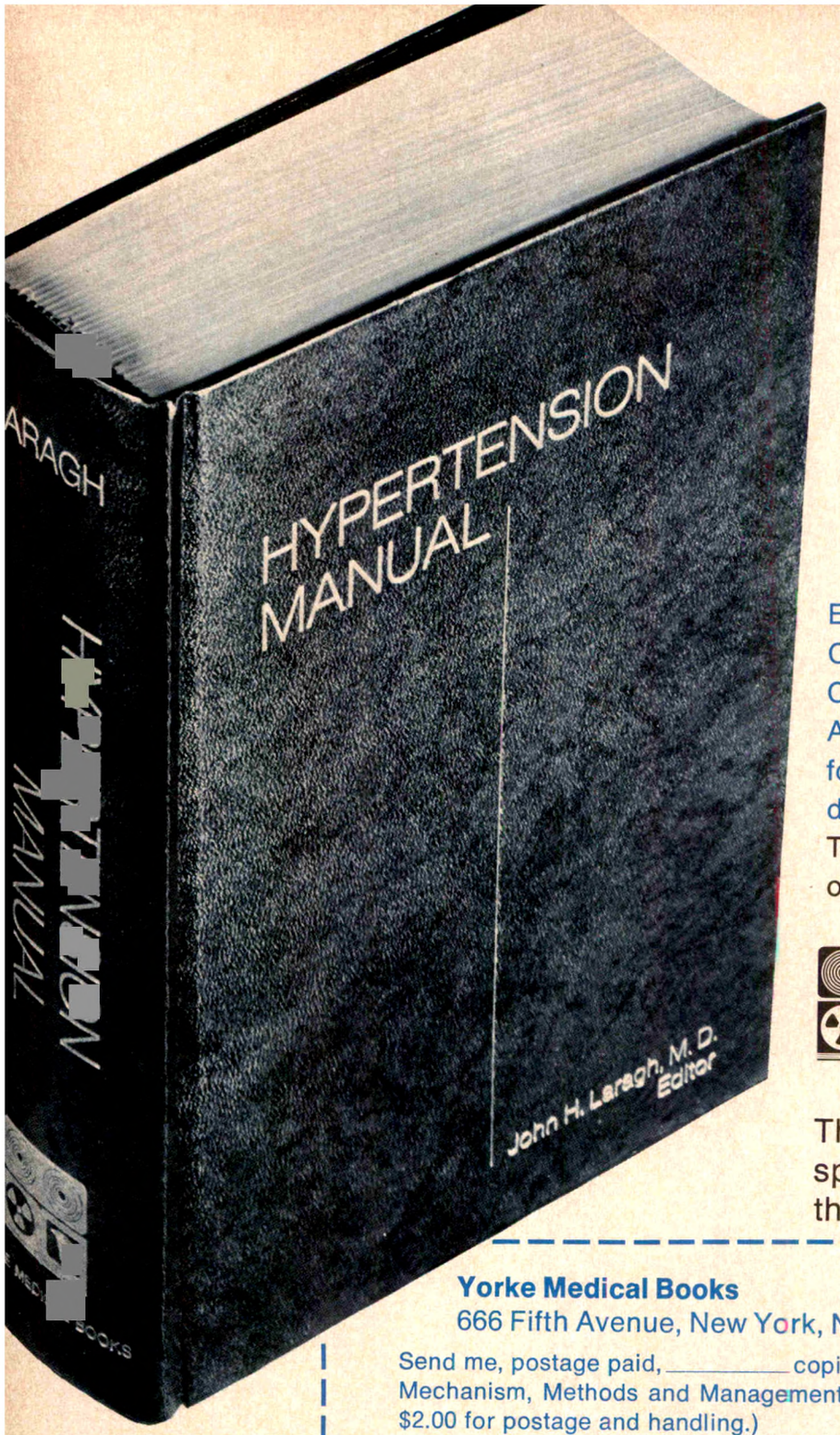

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■ Antihypertensive Drug Therapy
■ Moderate Low Sodium Diet

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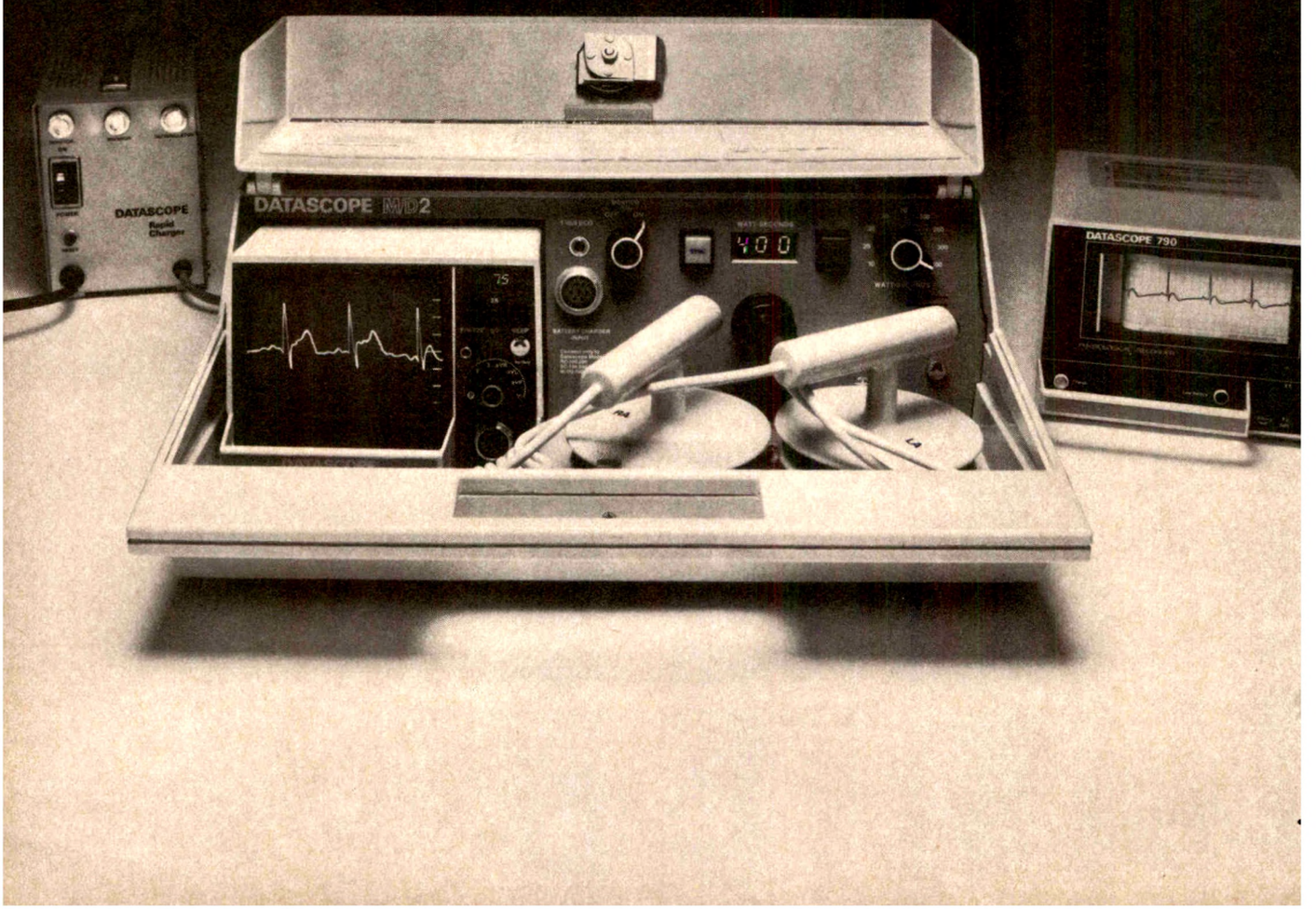


If there's one thing you can be sure of in cardiac rescue, it's that you can't be sure of anything.

Every situation, either in the hospital or in the field, presents new problems, and requires new solutions.

At Datascope, we've been in emergency medicine since its inception.

Our equipment has faced just about everything. And from that experience we've put together a system that's prepared to face anything: the M/D2 System.

The M/D2 System is built on one very simple principle. *Every instrument in the system must be independent and not compromised by any other instrument.*

In keeping with this philosophy, our monitor, our defibrillator and our strip-chart recorder each have a separate battery source. One unit never puts a drain on another.

But to see its flexibility, let's take our system apart, instrument by instrument.

OUR MONITOR.

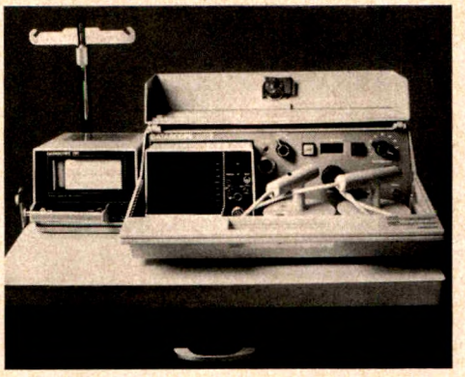
The monitor in the M/D2 System nests inside the defibrillator. You can carry the monitor and defibrillator, use it, and store it as one unit.

But the monitor pulls out* of the M/D2 case and works as a separate unit as well. So it can be placed right on a patient's stretcher in the field. Or put in the most advantageous viewing position at the bedside.

U.S. PATENT 3,865,101

In addition to being so flexible, our monitor outperforms any monitor in emergency medicine.

It has a 5-inch scope with a 8 x 11 cm. viewing area.



It has a memory which provides a bright, non-fade display that's remarkably clear even in strong sunlight.

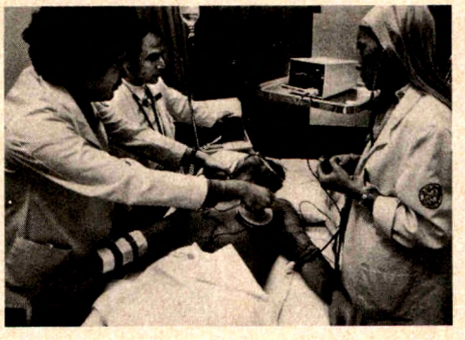
It has a freeze button which lets you stop the ECG for closer study.

It's the only emergency monitor with a digital heart rate readout. And because the readout is an LED display, you can even read it in the dark.

OUR DEFIBRILLATOR.

Like our monitor, our defibrillator has its own battery-pack.

It's the only defibrillator made that gives you a *digital* energy meter. Which displays both stored energy and the results of delivered energy tests.



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Energy cannot be delivered unless the push-button switch on each paddle is actuated simultaneously.

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For paramedic use, the M/D2 is available completely shielded against RF interference across the entire communications band.

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Our recorder is flexible as well. It's carried separately and powered separately. (For good reason. A recorder powered by a common battery puts an enormous drain on the other instruments in the system.)

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Although the M/D2 comes with a standard battery recharger, we offer the first rapid recharging unit as part of our system. Our Rapid Charger allows you to defibrillate with just 60 seconds of recharge. And in just 10 minutes it will recharge the defibrillator to at least 60% of total capacity.

THE SYSTEM. IT'S MORE THAN ANY OF ITS PARTS.

Three independent units. Three independent battery-packs And a Rapid Charger. They work together, or apart. They give you more ability to react than any single unit ever could.

For more information on the M/D2 System, write: Datascope Corp., 580 Winters Avenue, Paramus, N.J. 07652.

THE DATASCOPE M/D2

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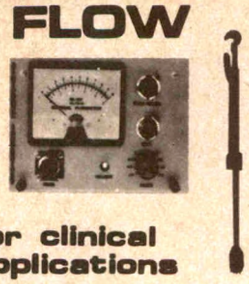

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- Designed for clinical O.R. or cath lab use
- Easily applied handle-type probe
- Patient safety assured through isolation circuitry
- Simple to operate - minimum controls - direct meter readout in milliliters per minute

FLOW PROBES

for clinical applications

- Convenient, handle-type probe with positive capture slide
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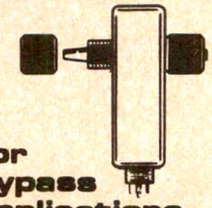

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- Use with heart-lung machine, artificial kidney or similar systems
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Physiological Adaptation to the Environment

F. J. Vernberg, Editor

Admirably fulfills the need for a definitive review of recently acquired information on the mechanisms of physiological adaptation as they relate to molecular, organismic, and ecosystem levels of biological organization. This carefully edited treatise is based on the several sessions of the symposium on adaptive behavior held before standing-room-only audiences at the AIBS meetings at the University of Massachusetts in June of 1973. Many of the 40 participants would not normally have contact with each other, and the sections of the symposium were planned by representative of 16 societies and research stations.

This volume, which should provide many useful insights and guides to future research, is comprised of six sections. Section I deals with the general nature of physiological adaptation. Sections II-IV cover organisms in desert, polar-alpine, and aquatic habitats. The fifth section focuses on the adaptive nature of biological time measurements, and the volume concludes with papers on the positive and negative aspects of modelling and on the interaction of multiple factors on plants and animals.

July, 1975 **about 500 Pages**
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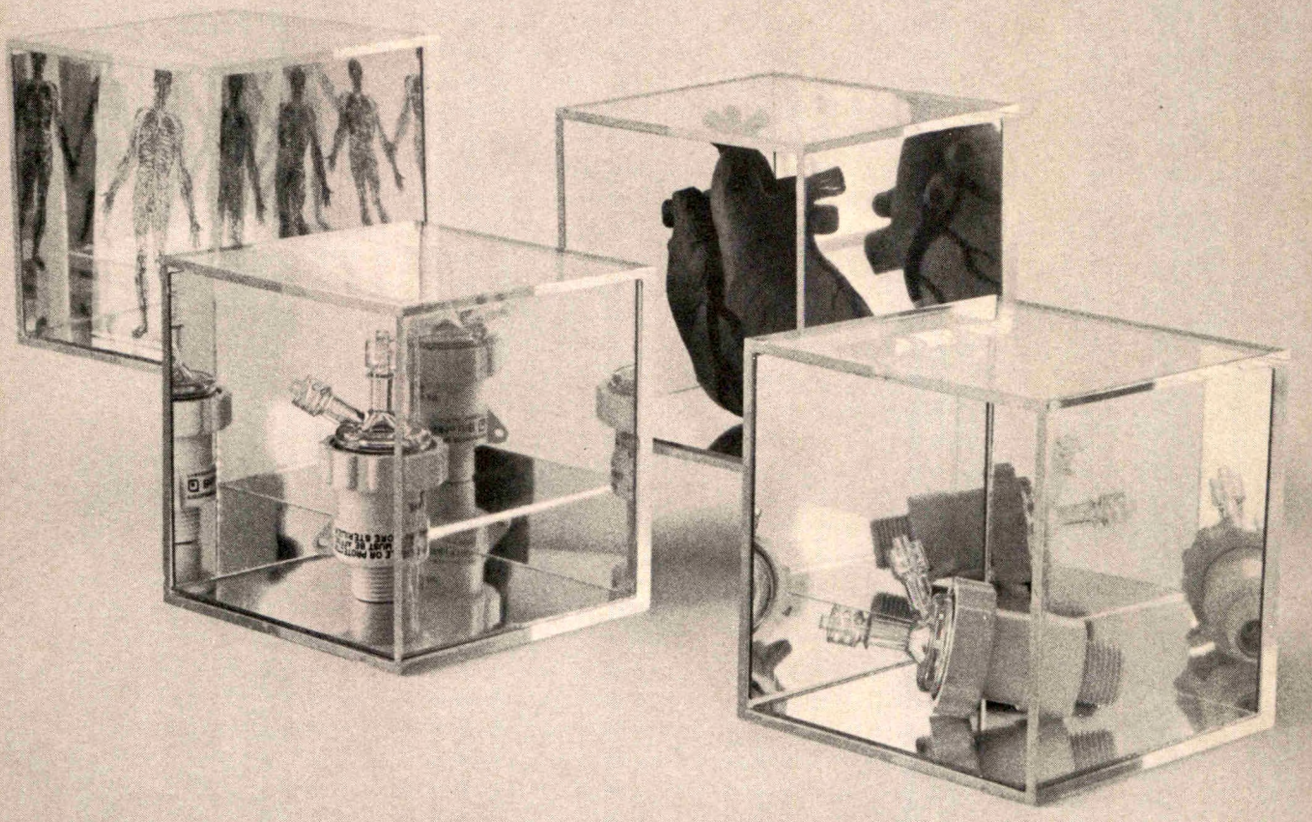

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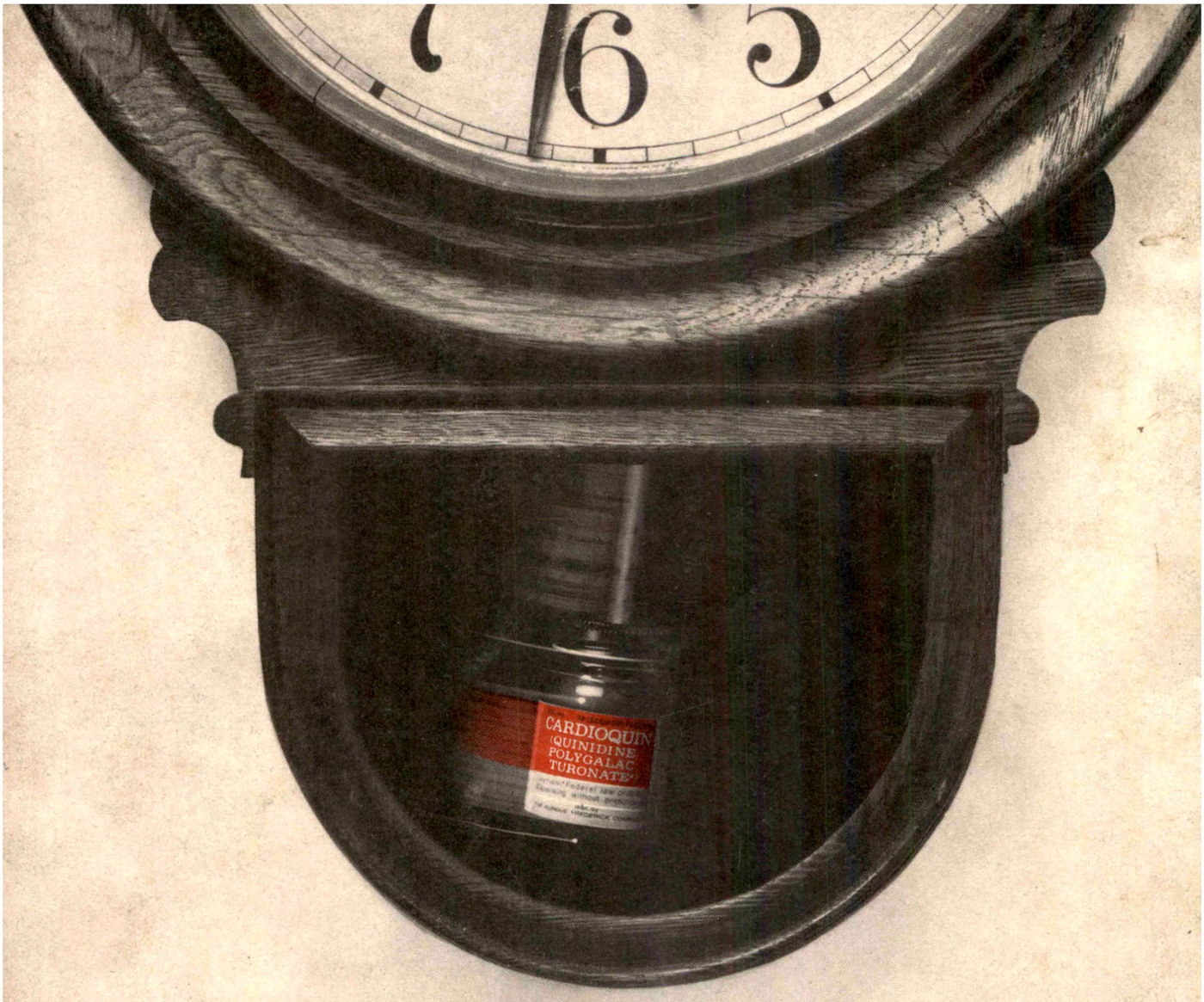

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

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AUGUST 1975

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Left Main Coronary Artery Disease

Symposium on Reperfusion During Acute Myocardial Infarction—Part I
Samuel Meerbaum, PhD, FACC and Eliot Corday, MD, FACC, Guest Editors

Call for Abstracts: ACC 25th Annual Scientific Session
New Orleans, Louisiana, February 23-26, 1976

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In hypertension—
Once you have found him...

TABLETS, 25 mg and 50 mg

HydroDIURIL®

(HYDROCHLOROTHIAZIDE | MSD)

a basic therapeutic approach to hypertension

The importance of early diagnosis in hypertension, so that appropriate treatment can be initiated promptly, has been well established.

Authorities in cardiovascular medicine have come more and more to favor the thiazides as initial drug therapy in early essential hypertension—for several important reasons.

initial medication that is often effective when used alone

The thiazides are well-established baseline therapy. Their effectiveness in lowering blood pressure has been thoroughly documented, and this effectiveness fits the needs of most patients with mild hypertension. Many hypertensives can be maintained for years on thiazide therapy.

suitable when used with other agents

Equally important is the usefulness of the thiazides in combination with other antihypertensive agents, when they are indicated. This retention of the thiazide in the regimen provides a useful baseline upon which the physician may build a therapeutic program. Since thiazides may add to or potentiate the action of other antihypertensive drugs, careful observation for changes in blood pressure must be made.

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For a brief summary of prescribing information, please see following page.

MSD
MERCK SHARP & DOHME

Once you have found him...

HydroDIURIL®

(HYDROCHLOROTHIAZIDE | MSD)

in the management of hypertension

Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs; routine use in an otherwise healthy pregnant woman with or without mild edema.

Warnings: Use with caution in severe renal disease since thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Use in pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy or in women of childbearing potential, weigh anticipated benefit against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.

Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 25 mg hydrochlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 50 mg hydrochlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Tablets containing 100 mg hydrochlorothiazide each in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

addendum

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"Required Reading" For Your Hypertensive Patients

Because of the importance of patient motivation, Merck Sharp & Dohme offers "High Blood Pressure," a concise, pocket-sized booklet that defines the patient's own role in the management of hypertension. This booklet is available for you to give to your patients. It is designed to reinforce your explanation of hypertension and it emphasizes the importance of patient understanding in adhering to the regimen you prescribe.

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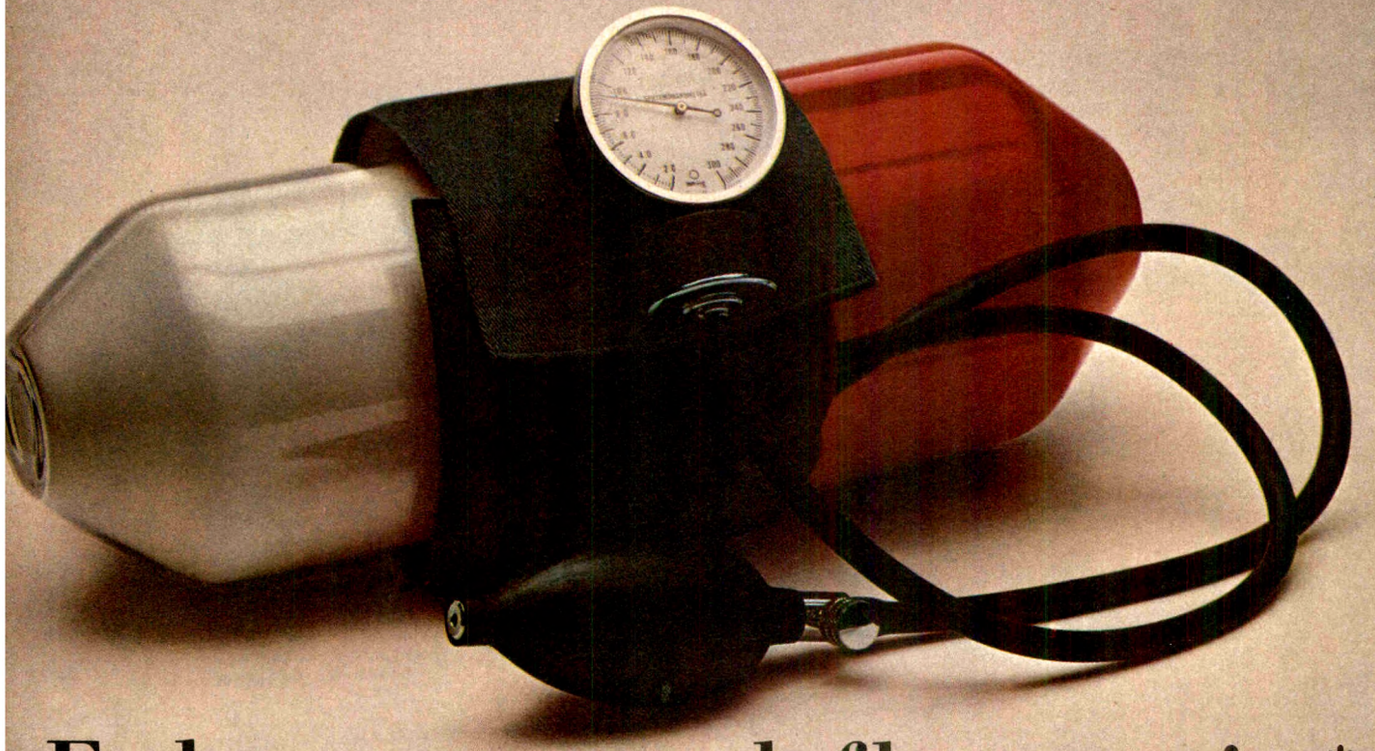

For long-term control of hypertension*

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **WARNING**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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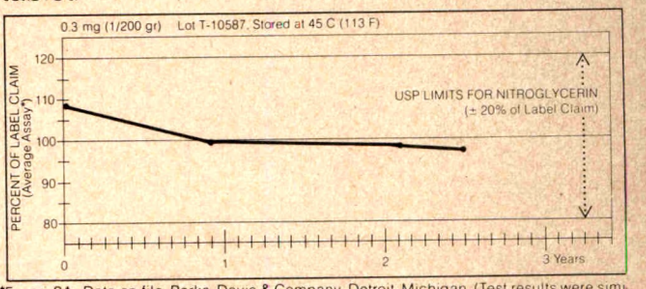

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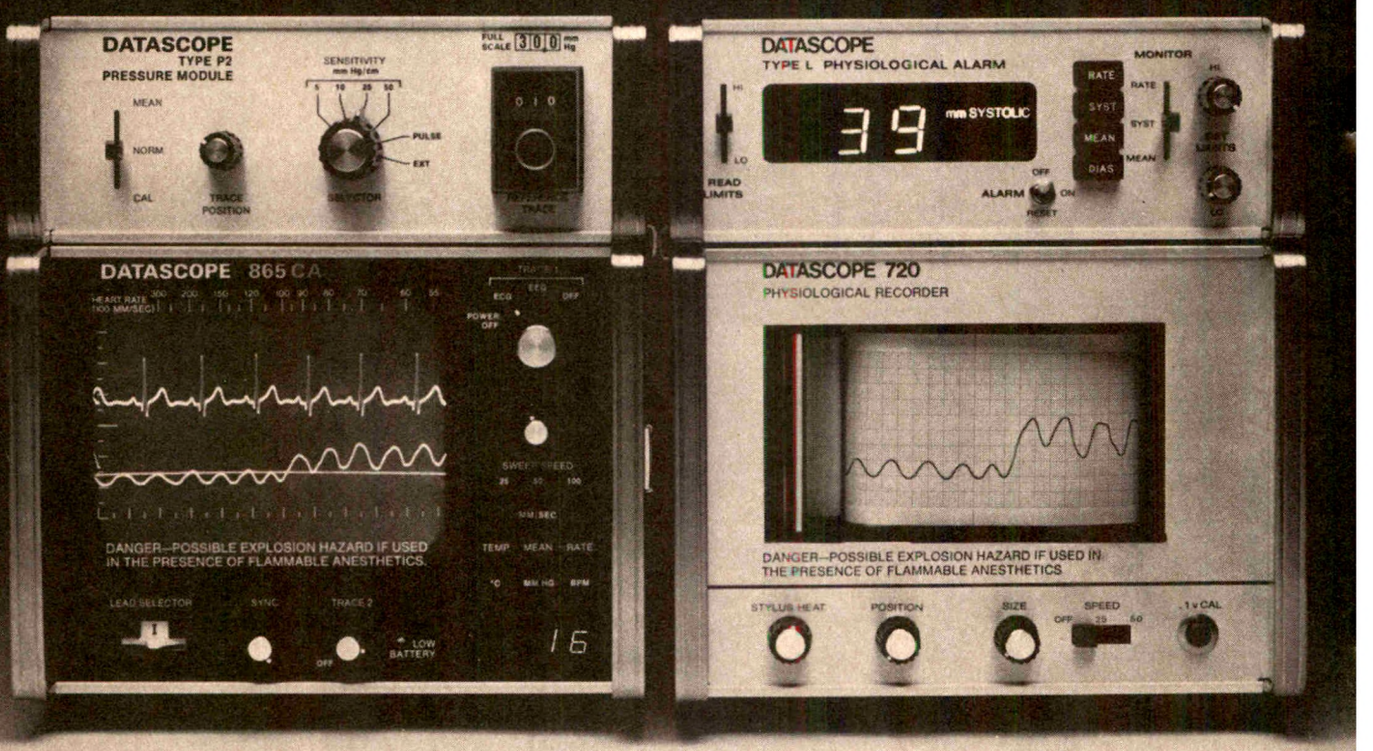

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225 **Experimental Coronary Arterial Occlusion and Release. Effects on Enzymes, Electrocardiograms, Myocardial Contractility and Reactive Hyperemia.** Marvin Richard Blumenthal, Hsueh-Hwa Wang and Letty Mei Pang Liu

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

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AUGUST 1975

The American Journal of CARDIOLOGY®

VOLUME 36

NUMBER 2

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CLINICAL STUDIES

131 Left Main Coronary Arterial Obstruction: Long-Term Follow-Up of 141 Nonsurgical Cases

JUAN S. LIM, WILLIAM L. PROUDFIT AND F. MASON SONES, Jr.

In 141 patients with obstructive left main coronary artery disease followed up 5 to 10 years from the date of coronary arteriography, left ventricular hypertrophy, conduction delay in the electrocardiogram and multiple vessel involvement were most common in those dying in the 1st year after diagnosis. Severe angina pectoris, congestive heart failure and decreased left ventricular contractility increased the 5 year mortality rate.

136 Left Main Coronary Artery Disease. Risks of Angiography, Importance of Coexisting Disease of Other Coronary Arteries and Effects of Revascularization

HENRY DeMOTS, LAWRENCE I. BONCHEK, JOSEF RÖSCH, RICHARD P. ANDERSON, ALBERT STARR and SHAHBUDIN H. RAHIMTOOLA

This clinical and angiographic analysis of 58 patients with left main coronary artery disease studied between September 1967 and June 1974 shows that coronary arteriography by the Judkins technique had a low risk. Presence of the disease could not be reliably predicted before arteriography. Coexisting disease in other major coronary arteries constituted an important determinant of the poor prognosis of such patients and precluded surgery in 13 percent. Surgical therapy relieved symptoms more effectively than nonsurgical therapy.

142 Variant Angina Pectoris: Clinical and Anatomic Spectrum and Results of Coronary Bypass Surgery

SAMUEL J. SHUBROOKS, Jr., JOHN M. BETE, ADOLPH M. HUTTER, Jr., PETER C. BLOCK, MORTIMER J. BUCKLEY, WILLARD M. DAGGETT and ELDRED D. MUNDTH

Experience with 20 patients suffering from the variant angina syndrome indicates that all such patients should be studied by coronary angiography. Seventeen patients had significant proximal stenosis of one or more coronary arteries with good distal vessels. Bypass surgery in 15 patients resulted in one noncardiac postoperative death, one myocardial infarction during surgery and long-term relief of pain in all 14 survivors. The three patients without significant coronary artery disease could not be distinguished clinically from those with severe obstructive disease.

148 Oxygen Delivery, Anoxic Metabolism and Hemoglobin Oxygen Affinity (P_{50}) in Patients with Acute Myocardial Infarction and Shock

PROTASIO L. da LUZ, JOSE M. CAVANILLES, SYBIL MICHAELS, MAX HARRY WEIL and HERBERT SHUBIN

A compensatory increase in P_{50} observed in patients with reduced oxygen delivery after acute myocardial infarction supplies an estimated 18 percent increase in oxygen availability. This increase in P_{50} and oxygen availability, independent of changes in cardiac output, is contingent on the presence of other factors, including peripheral shunting and cellular capacity to take up oxygen at a given time.

Continued on page A13

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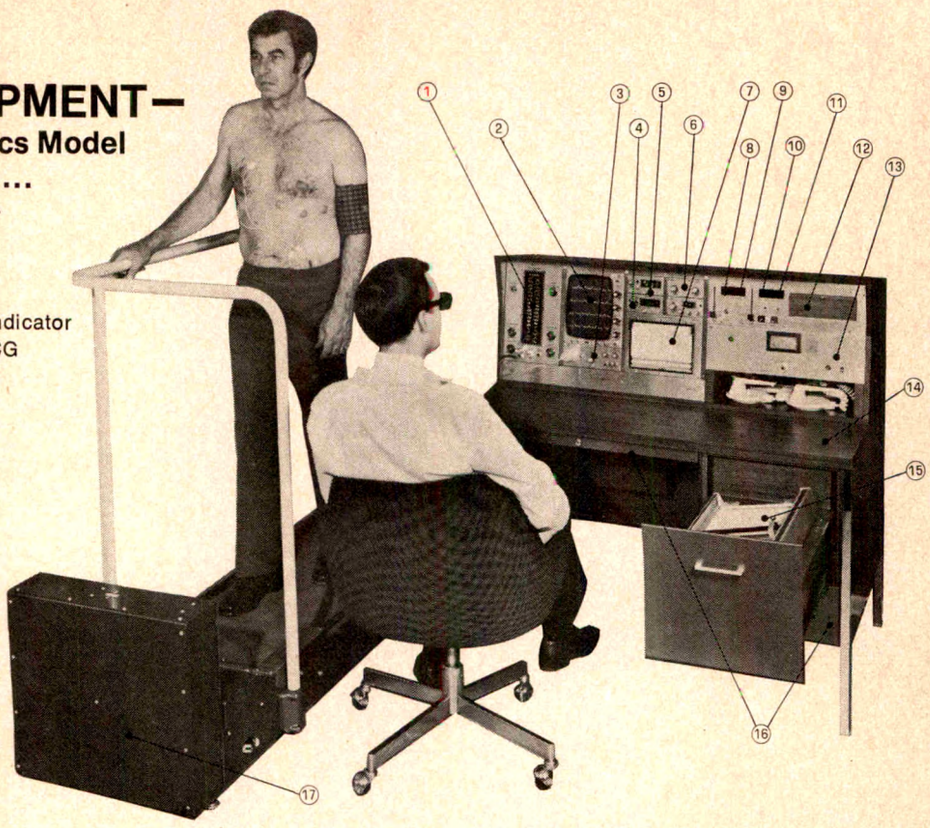

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155 Measurement of S-T Segment Elevation in Acute Myocardial Infarction in Man. Comparison of a Precordial Mapping Technique and the Frank Vector System

TOSHIO AKIYAMA, MORRISON HODGES, THEODORE L. BIDDLE, BARBARA ZAWROTNY and CATHERINE VANGELLOW

Estimation of the magnitude and direction of the S-T vector derived from the X, Y and Z leads of the Frank vector system serves as a simple alternative to standard precordial S-T segment mapping and allows for continuous monitoring of S-T segment elevations in all patients with acute myocardial infarction, whether the infarction involves the inferior or anterior wall of the left ventricle.

163 Reappearance of Anterior QRS Forces After Coronary Bypass Surgery. An Electrovectorcardiographic Study

HOWARD J. ZEFT, H. DAVID FRIEDBERG, JAMES F. KING, JACK C. MANLEY, JOHN H. HUSTON and W. DUDLEY JOHNSON

Electrocardiographic and vectorcardiographic studies in six patients with typical patterns of transmural anterior wall myocardial infarction with Q waves in the right precordial leads showed regeneration of R waves in these leads and loss of the pattern of definite infarction within 10 days after direct coronary arterial bypass surgery. These studies demonstrate the reversibility of the electrical patterns of myocardial infarction in some patients upon reestablishment of perfusion to ischemic areas.

169 Significant Sex Differences in the Correlation of Electrocardiographic Exercise Testing and Coronary Arteriograms

MICHAEL H. SKETCH, SYED M. MOHIUDDIN, JOSEPH D. LYNCH, ALLEN E. ZENCKA and VINCENT RUNCO

A positive multistage stress test is useful in men but not in women in predicting significant coronary artery disease prior to arteriography. On the other hand, a negative stress test is useful in ruling out such disease in women but not in men. There is no clear explanation for this sex difference and for the high incidence rate (67 percent) of false positive stress tests in women.

174 Comparison of Angiographic and Postmortem Findings in Patients with Coronary Artery Disease

JARED N. SCHWARTZ, YIHONG KONG, DONALD B. HACKEL and ALAN G. BARTEL

Premortem cineangiographic studies of coronary artery stenosis in 25 patients were in agreement with autopsy findings in 79 percent of the segments examined, overestimated it in 6 percent and underestimated it in 15 percent. This confirms the reliability of coronary arteriography in evaluating the severity of coronary artery disease. Common causes of error, particularly of underestimation, included circumferential stenosis, eccentric lesions, obstruction of view by artificial valves and poor opacification because of severe proximal stenosis.

EXPERIMENTAL STUDIES

179 Effect of Practolol on Left Ventricular Dimensions During Coronary Occlusion

JON LEKVEN

Practolol, a relatively cardiospecific beta blocking agent, given to dogs during acute coronary arterial occlusion, reduced myocardial dilatation and increased systolic shortening in ischemic areas. In nonischemic control regions it caused further dilatation and diminished shortening. Practolol thus improved function in ischemic ventricular regions and restored ventricular stroke volume, presumably as a result of improved myocardial oxygen balance.

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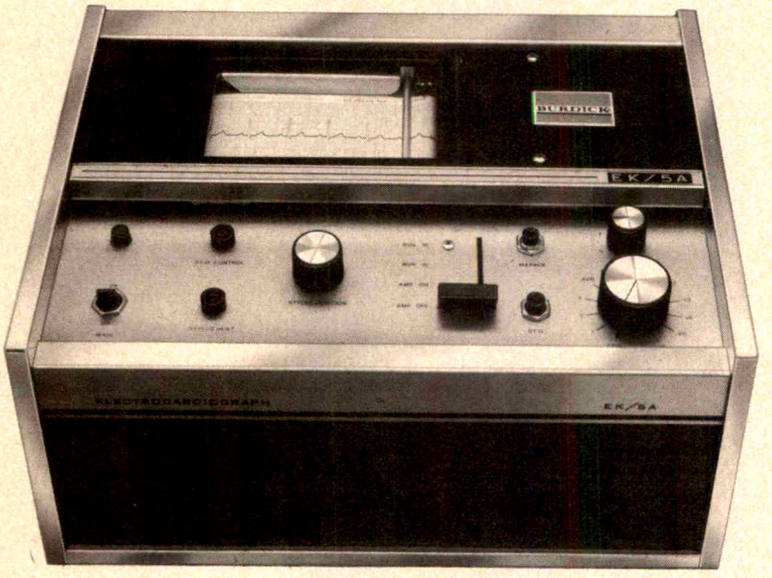

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185 Effect of Graded Reductions in Regional Coronary Perfusion on Regional and Total Cardiac Function

H. L. WYATT, JAMES S. FORRESTER, JOHN V. TYBERG, STEVEN GOLDNER, SAMUEL E. LOGAN, WILLIAM W. PARMLEY and H. J. C. SWAN

This study of graded reduction in regional coronary perfusion and in arterial oxygen concentration in 14 open heart dogs demonstrates that myocardial function depends upon a critical level of coronary perfusion pressure and flow. Regional function dropped sharply when coronary perfusion pressure and flow were reduced to 50 to 65 mm Hg and 25 to 55 ml/min per 100 g, respectively. Changing arterial oxygen concentration affected ventricular performance only at the low range of coronary perfusion pressure (±22 mm Hg).

METHODS

193 Diastolic Compliance of the Left Ventricle in Man

WILLIAM H. GAASCH, MIGUEL A. QUINONES, EFRAIN WAISSER, HANS G. THIEL and JAMES K. ALEXANDER

Pressure-volume data over a range of operating pressures are necessary for assessing left ventricular compliance. The product of end-diastolic stress and left ventricular linear compliance derived from volume compliance and normalized for left ventricular wall thickness provides a useful index of myocardial strain (muscle fiber stretch). This index may be related to systolic performance and allows comparison of length-performance relations in ventricles with normal and abnormal compliance.

REPORTS ON THERAPY

202 Hemodynamic Effect of Dobutamine in Patients with Severe Heart Failure

NASIM AKHTAR, ESTEBAN MIKULIC, JAY N. COHN and M. HAFEEZ CHAUDHRY

Dobutamine, a derivative of dopamine, demonstrated potent inotropic, but limited chronotropic and peripheral vascular, effects in 15 patients with severe congestive heart failure. Cardiac output was significantly increased with no or only slight change in arterial pressure and heart rate. These results justify further therapeutic trial in the short-term management of low output heart failure, particularly in older patients with ischemic heart disease.

206 Effects of Isosorbide Dinitrate on the Response to Atrial Pacing in Coronary Heart Disease

ROBERT J. STEELE, GARY W. BURGGRAF and JOHN O. PARKER

The sublingual administration of 5 mg of isosorbide dinitrate to 20 patients with angiographically proved coronary artery disease provided a significant protective effect against pacing-induced myocardial ischemia at 10 and 65 minutes after its administration. This was demonstrated by prevention of or decrease in severity of angina and S-T segment depression, an increase in lactate extraction, and a significant decrease in left ventricular end-diastolic pressure after isosorbide dinitrate administration.

SYMPOSIUM ON REPERFUSION DURING ACUTE MYOCARDIAL INFARCTION. PART I

211 Introduction

SAMUEL MEERBAUM and ELIOT CORDAY

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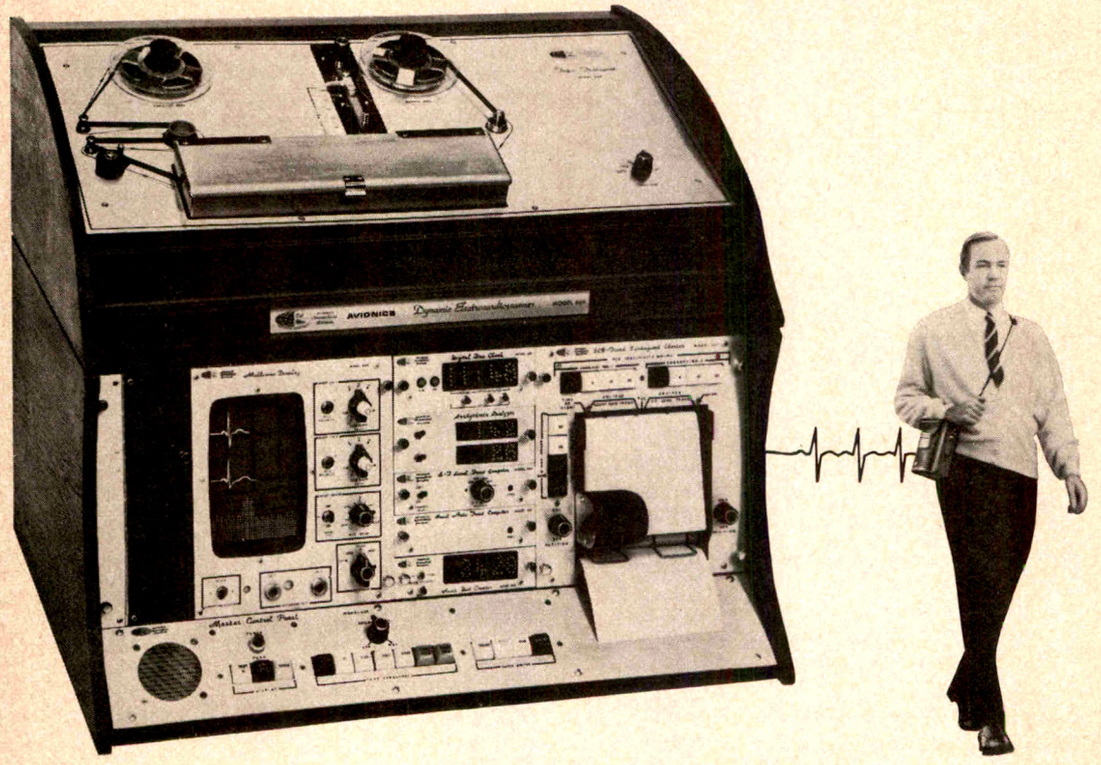

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214 Alterations in Myocardial Hydrogen Ion Concentration After Temporary Coronary Occlusion: A Sign of Irreversible Cell Damage

ARNO KRUG

The hydrogen ion (H^+) concentration increased (pH <6.0) in a transmural extension in the left ventricle of cats after ligation of the left anterior descending coronary artery and diminished (pH 7.4) in the border zone between the acid-reacting area and the normal muscle. The persistence of the elevated H^+ concentration in the subendocardial region despite release of the coronary occlusion proves lack of reestablishment of blood flow (no reflow phenomenon) in the involved myocardium after temporary coronary occlusion. This indicates persistent ischemia in involved myocardium despite release of the temporary coronary occlusion. An alkaline reaction of the myocardium is an early indicator of irreversible muscle cell damage.

218 Mitochondrial Function, Oxygen Extraction, Epicardial S-T Segment Changes and Tritiated Digoxin Distribution After Reperfusion of Ischemic Myocardium

JAMES J. KANE, MARVIN L. MURPHY, JOE K. BISSETT, NEIL deSOYZA, JAMES E. DOHERTY and KARL D. STRAUB

Reperfusion for 2 hours failed to improve the indexes of myocardial viability or prevent necrosis after 60 minutes or more of myocardial ischemia in pigs. These results call for caution and critical evaluation of early surgical revascularization as treatment for acute myocardial ischemia or infarction in man.

225 Experimental Coronary Arterial Occlusion and Release. Effects on Enzymes, Electrocardiograms, Myocardial Contractility and Reactive Hyperemia

MARVIN RICHARD BLUMENTHAL, HSUEH-HWA WANG and LETTY MEI PANG LIU

In dogs whose left anterior descending coronary artery was experimentally occluded for 1 to 3 hours and then released, coronary venous and serum enzymes increased within 10 to 20 minutes and significant Q waves appeared within 15 to 30 minutes after release of the occlusion. Thus, clinically, the delayed appearance of serum enzyme elevation and Q waves is attributed largely to a lack of circulation in the infarcted area rather than to prolonged survival time. Viability of myocardium was suggested by S-T elevation after reclamping and by residual contractility and reactive hyperemia.

234 Alterations in Energy Metabolism and Ultrastructure Upon Reperfusion of the Ischemic Myocardium After Coronary Occlusion

GYAN P. SHARMA, KENNETH G. VARLEY, SUNG W. KIM, JAROSLAW BARWINSKY, MORLEY COHEN and NARANJAN S. DHALLA

In 48 dogs changes in myocardial function, metabolism and ultrastructure brought about by 30 minutes, and possibly 60 minutes, of myocardial ischemia were reversible after 60 minutes of reperfusion. Ninety minutes of ischemia caused severe irreversible myocardial damage, as indicated by levels of creatine phosphokinase, glutamic oxaloacetic transaminase and lactic dehydrogenase in the coronary sinus blood and changes in the mitochondria and sarcoplasmic reticulum.

244 Contractile and Biochemical Effects of Coronary Reperfusion After Extended Periods of Coronary Occlusion

PRITPAL S. PURI

With coronary occlusion of 1 to 3 hours' duration, myocardial contractility failed to return in the immediate postperfusion period, but delayed recovery was recorded after 2 weeks of reperfusion. High energy phosphate content of the reperfused myocardium showed a similar pattern of recovery. The extent of recovery varies inversely with the duration of occlusion.

Continued on page A19

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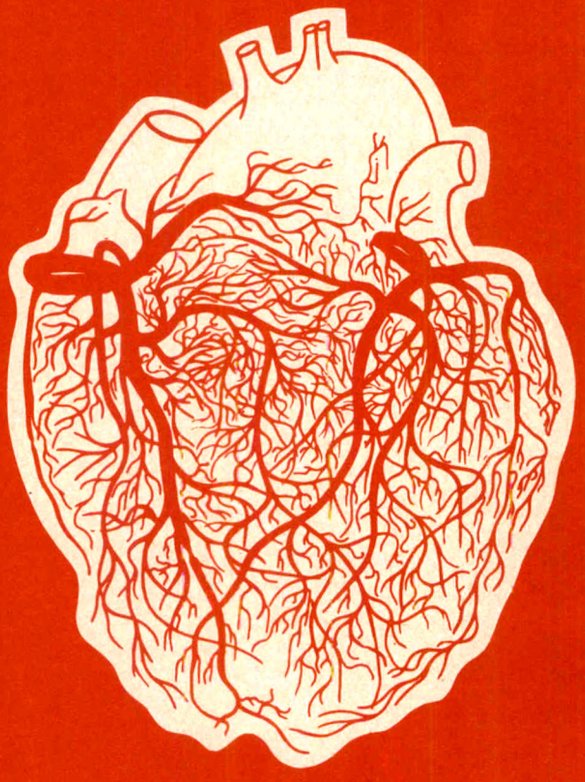

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***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.
Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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252 **Maximal Revascularization (Reperfusion) in Intact Conscious Dogs After 2 to 5 Hours of Coronary Occlusion**

VIRENDRA S. MATHUR, GENE A. GUINN and WALTER H. BURRIS, III

Reperfusion in 56 intact conscious dogs following 2 and 5 hours of left anterior descending coronary occlusion not only did not fail to prevent deterioration and death, but also hastened the development of arrhythmias and myocardial injury. Infarct size can be reduced by reperfusion if performed after 2 hours but not after 5 hours, of occlusion. More studies using other species are indicated before any large scale surgical revascularization is attempted in the early stage of myocardial infarction in man.

CASE REPORTS

262 **Successful Partial Excision of an Intramural Fibroma of the Left Ventricle**

GEORGE J. REUL, Jr., JIMMY F. HOWELL, PEDRO A. RUBIO and PAUL K. PETERSON

Simulating mitral stenosis and insufficiency for years, a massive intramural fibroma of the posterior wall of the left ventricle and most of the interventricular septum was partially excised with good results in a 31 year old man with syncopal episodes and chest pain of 4 years' duration. A left ventricular angiogram demonstrated the calcified lesion preoperatively.

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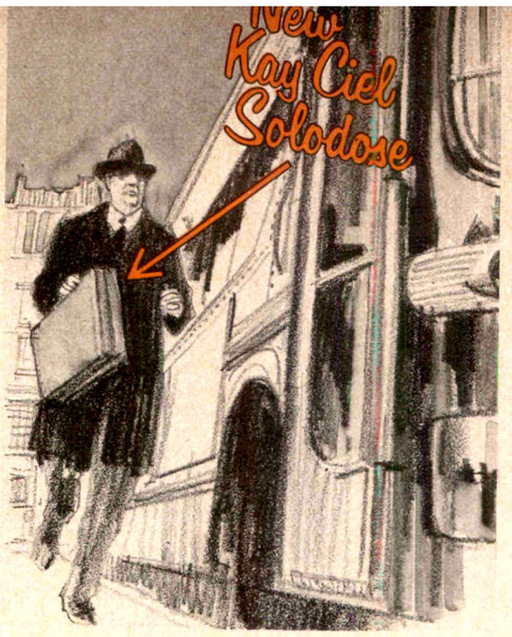

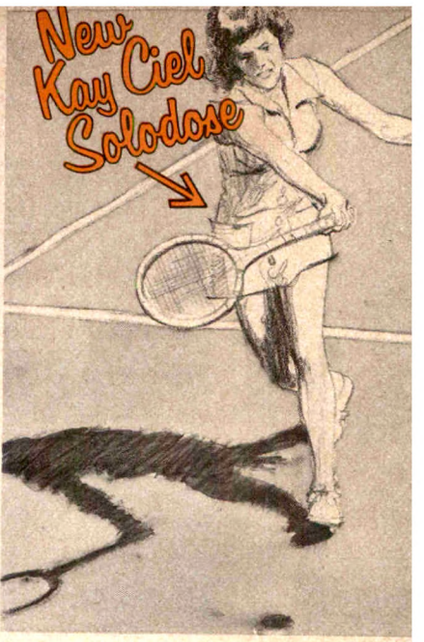

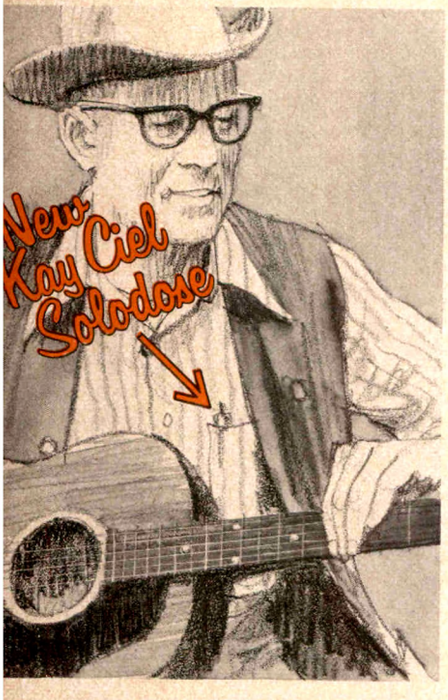

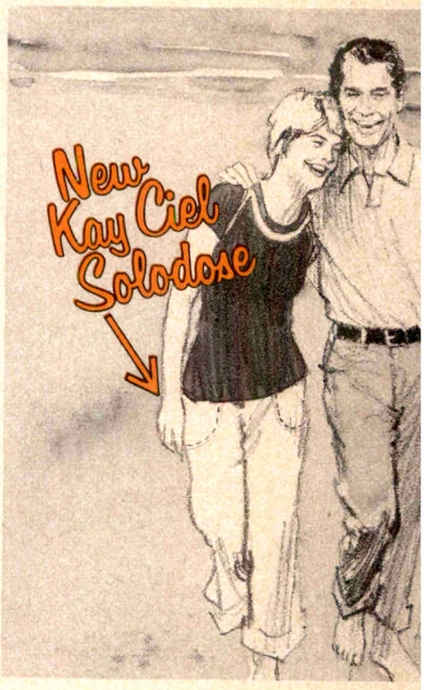

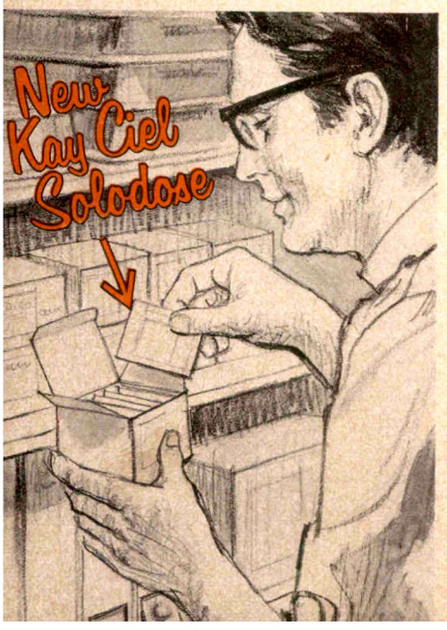

Portable Potassium Chloride

New KAY CIEL®

(potassium chloride, 1.5g.)

Solodose™ Powder

Each Solodose packet contains:
Potassium Chloride . . . 1.5 g. (20 meq.)
Flavored. Contains no sugar.

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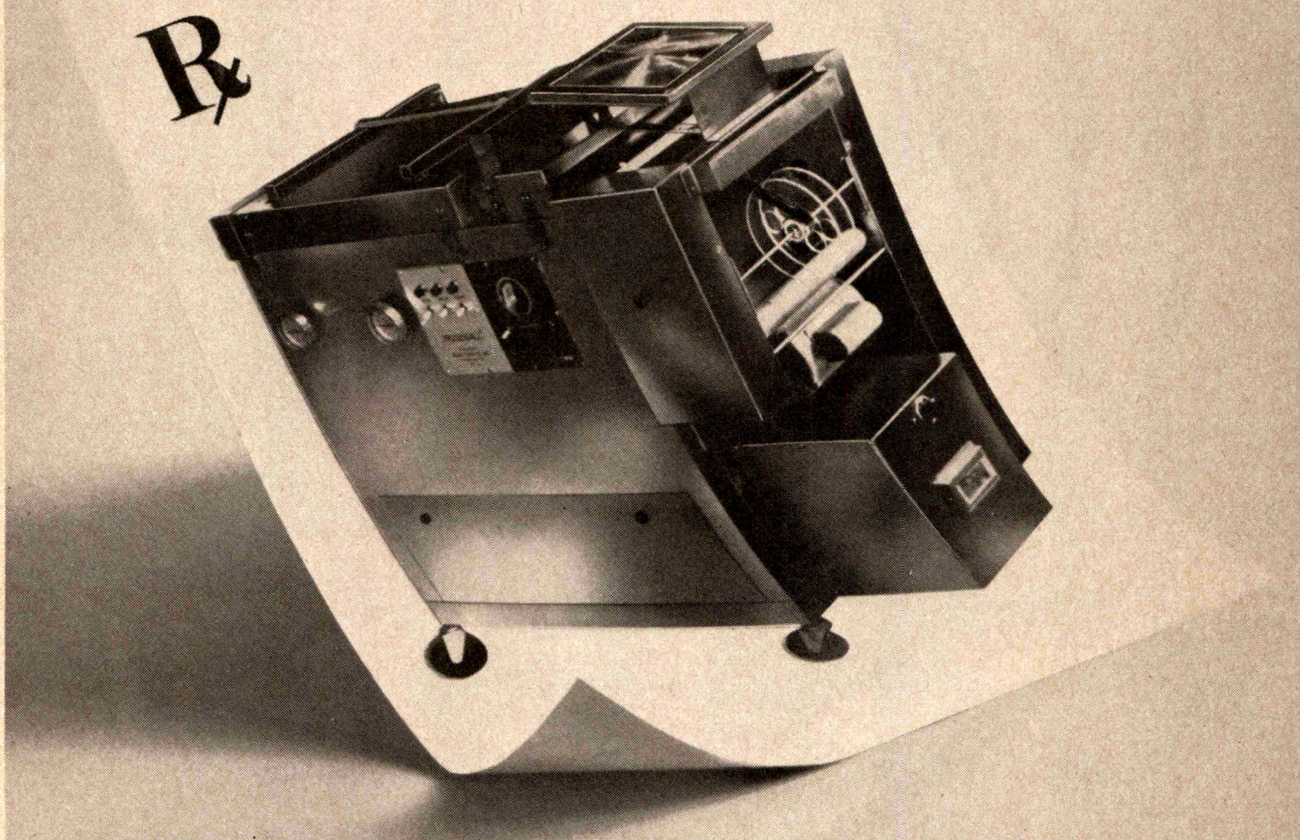
PROCESSALL

A Processor for Diagnostic Cine-Fluorography



The Processall yields fine grain, high acutance, superior resolution and full detail permitting an accurate diagnosis. Artifacts do not occur. Rapid, repeatable, excellent results are secured with ease. Speed is variable permitting pre-selection of desired density and contrast.

The Processall is self-threading and daylight operated. It is designed for ease of operation and maximum reliability with minimal maintenance required. Photosensitive films and papers in roll form may be processed dry-to-dry with a minimum of operator training.

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All models are compact, portable, and fit almost anywhere.

Most major medical centers and hospitals are using the Processall to fulfill their processing requirements.

The Mark 16/35 Processor for faster production (develops one 200 foot case every eight minutes) is also available.

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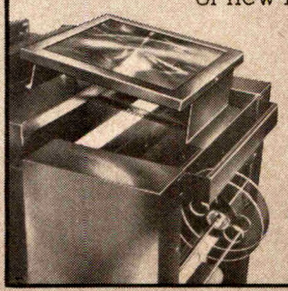
Instant Viewer*
now available for existing or new machines



*Inspect film as it exits the processor.

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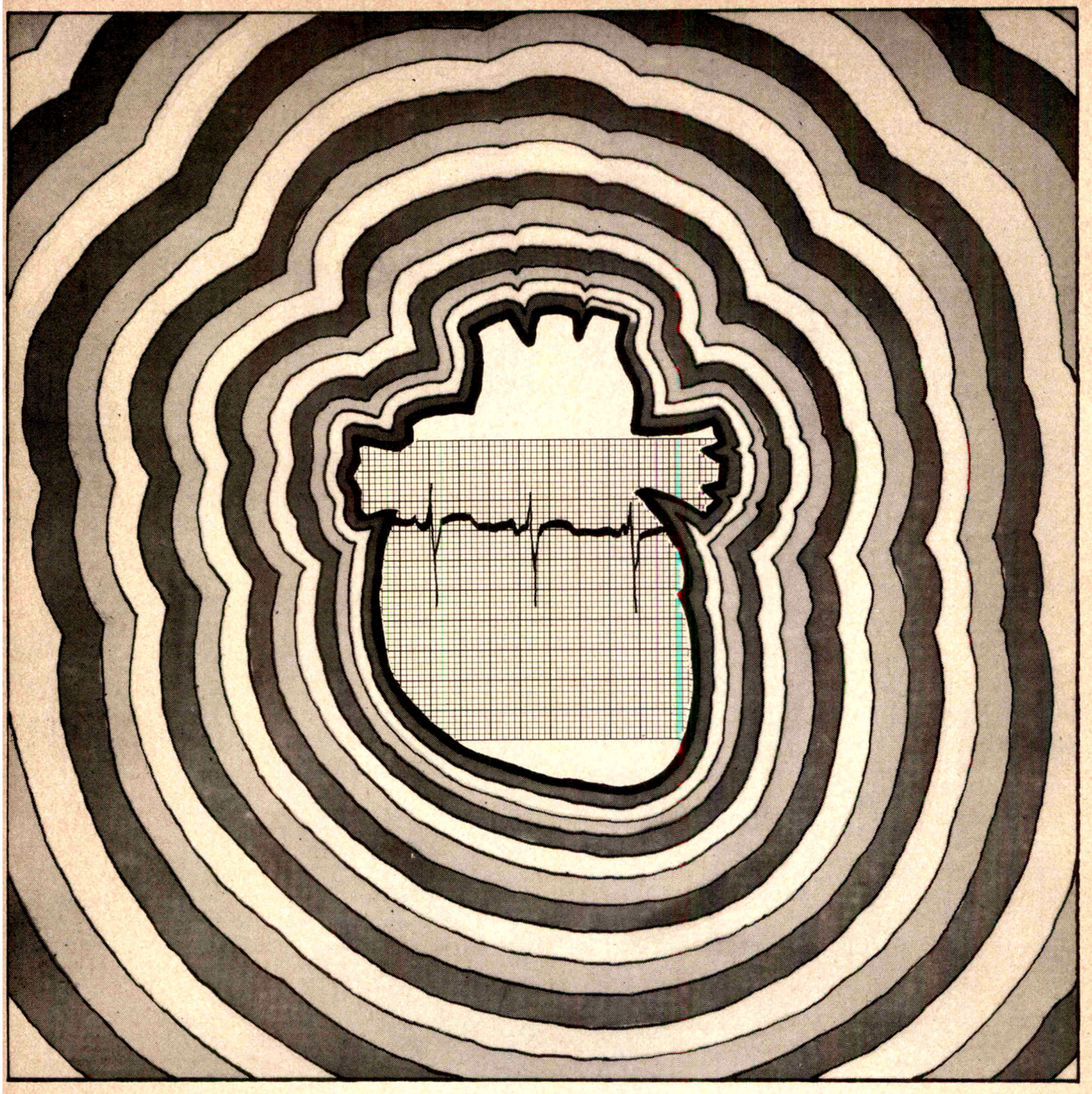
P.O. BOX 2305 / NEWBURGH, N.Y. 12550 TELEPHONE (914) 562-3900



the heart of your electrocardiograph diagnosis is made of paper

Accurate interpretation of analytical data presented by your electrocardiograph and subsequent proper diagnosis is manifested by the chart paper.

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Schering

Stat regimen for rapid reduction of blood pressure in malignant hypertension

direct-action **Hyperstat®** I.V.
Brand of DIAZOXIDE
INJECTION
20 ml ampule
contains 300 mg

"The injection of the [diazoxide] bolus in 10 to 15 seconds results in a prompt blood pressure fall in a high percentage of cases. A maximal blood pressure response usually occurs within 5 to 10 minutes."*

☐ **Rapid reduction to normotensive levels**

Induces rapid reduction of blood pressure generally within 5 minutes... often in 1 or 2 minutes to the lowest level achieved. Blood pressure response facilitated by appropriate diuretic therapy.

☐ **Prolonged activity**

A single injection of HYPERSTAT I.V. generally maintains blood pressure below pretreatment levels for periods up to 12 hours.

☐ **Protective action—helps avert target organ damage**

Cardiac output increases as diastolic pressure is reduced. Coronary and cerebral blood flow maintained. Increased renal blood flow after transient decrease.

☐ **Uncomplicated procedure**

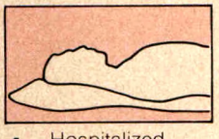
Simple I.V. "push" in a peripheral vein in 30 seconds or less. Close monitoring at frequent intervals is necessary until blood pressure is stabilized (generally 15-30 minutes). Thereafter, hourly measurement should be taken during the balance of effect.

☐ **Stable...convenient...no preparation**

HYPERSTAT I.V. Injection supplied in a 20 ml. ampule containing a stable solution of diazoxide 300 mg. ...ready to use.

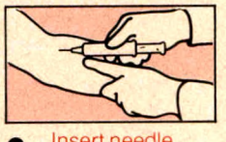
*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J* 87(6): 791-795, June 1974.

Administration guidelines



1. Hospitalized patient should be recumbent.

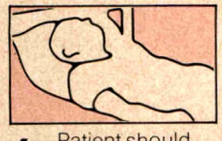
2. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml. ampule contains 300 mg. diazoxide).



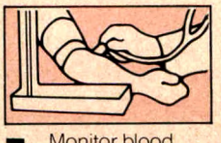
3. Insert needle only into a peripheral vein.

4. Inject entire dose I.V. in 30 seconds or less.

5. Remove needle carefully—avoid extravasation.

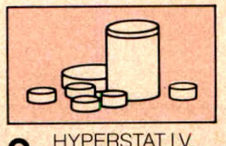


6. Patient should remain recumbent for at least half an hour after injection.



7. Monitor blood pressure closely until stabilized—usually 15-30 minutes.

8. If patient is to be ambulatory, blood pressure should be measured in standing position before surveillance is ended.



9. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective—generally within a few days.

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Before prescribing HYPERSTAT I.V. Injection, please consult complete product information on next page.

Stat regimen for rapid reduction of blood pressure in malignant hypertension

direct-action **Hyperstat®** I.V.

Brand of DIAZOXIDE

INJECTION
20 ml ampule
contains 300 mg

FOR INTRAVENOUS USE IN HOSPITALIZED PATIENTS ONLY

Description HYPERSTAT I.V. Injection is a rapidly acting antihypertensive agent. Each ampule (20 ml.) contains 300 mg. diazoxide, a nondiuretic benzothiadiazine derivative, in a clear, colorless, aqueous solution; the pH is adjusted to approximately 11.6 with sodium hydroxide. Diazoxide is 7-chloro-3-methyl-2H 1, 2, 4-benzothiadiazine 1, 1-dioxide.

Actions HYPERSTAT I.V. Injection produces a prompt reduction in blood pressure by relaxing smooth muscle in the peripheral arterioles. Cardiac output is increased as blood pressure is reduced by diazoxide; coronary and cerebral blood flow are maintained. Renal blood flow is increased after an initial decrease. Diazoxide has no known direct action on the central nervous system.

Patients refractory to other antihypertensive agents usually remain responsive to diazoxide.

Diazoxide is extensively bound to serum protein (>90%). The plasma half-life is 28 ±8.3 hours; however, the duration of its antihypertensive effect is variable, generally lasting less than 12 hours. Although an antihypertensive response has been obtained with slow intravenous injection, in general, a greater antihypertensive effect is obtained with rapid intravenous administration.

Indications HYPERSTAT I.V. Injection is indicated for the emergency reduction of blood pressure in malignant hypertension in hospitalized patients, when prompt and urgent decrease of diastolic pressure is required. Treatment with orally effective antihypertensive agents should be instituted as soon as the hypertensive emergency is controlled.

HYPERSTAT (diazoxide) I.V. Injection is ineffective against hypertension due to pheochromocytoma.

Contraindications HYPERSTAT I.V. Injection should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt.

The drug should not be used in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

Warnings **Usage in Pregnancy:** The safety of HYPERSTAT I.V. Injection in pregnancy has not yet been established.

Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults.

Usage in Children: The safety of HYPERSTAT I.V. Injection in children has not yet been established.

Hypotension may occasionally result from the administration of HYPERSTAT I.V. If hypotension severe enough to require therapy occurs, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine.

Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide.

Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. It should be noted that concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions).

Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent.

Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

Precautions HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available when HYPERSTAT I.V. Injection is used.

HYPERSTAT I.V. Injection should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively.

Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response.

As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental.

Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection.

Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

Adverse Reactions

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial and/or cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; unconsciousness, convulsions, paralysis, or confusion; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported.

Other adverse reactions: Nausea, vomiting, and/or abdominal discomfort; vasodilative phenomena, such as flushing, generalized or localized sensations of warmth, headache (sometimes throbbing), and sweating; orthostatic hypotension, lightheadedness, and weakness of short duration; supraventricular tachycardia and palpitation; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; nonanginal "tightness in the chest"; warmth or pain along the injected vein; cellulitis without sloughing and/or phlebitis at the site of extravasation; anorexia and alteration of taste; ileus; bradycardia; back pain; chest discomfort; dyspnea, choking sensation; apprehension or anxiety, malaise, and blurred vision occurred on single occasions; parotid swelling, salivation, lacrimation; ringing in the ears; diarrhea and constipation; increased nocturia; euphoria.

Drug Interactions Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

Overdosage Overdosage of HYPERSTAT I.V. Injection may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy of hyperglycemia.

Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

Animal Pharmacology and Toxicology In studies involving a number of species, including the rat, cat, dog, and monkey, diazoxide has been shown to exert significant antihypertensive actions through its direct effect on peripheral arterioles, which neither impairs cardiac function nor seriously diminishes perfusion of kidneys. In addition, in each species tested, including the rat, dog, and monkey, diazoxide elicits hyperglycemia, increased serum-free fatty acids and decreased plasma insulin levels by a mechanism thought to involve both suppression of insulin release and enhanced catecholamine action.

Although the data are not conclusive, reproduction and teratology studies in several species of animals indicate that diazoxide, when administered during the critical period of embryo formation, may interfere with normal fetal development, possibly through altered glucose metabolism. Parturition was occasionally prolonged in animals treated at term.

Dosage and Administration HYPERSTAT I.V. Injection is administered undiluted and rapidly by intravenous injection. It should only be given into a peripheral vein. Do not administer it intramuscularly, subcutaneously, or into body cavities. Avoid extravasation of the drug into subcutaneous tissues.

The response to HYPERSTAT I.V. Injection varies from patient to patient. Generally, blood pressure decreases within five minutes, often within one to two minutes, to the lowest level achieved. The blood pressure increases relatively rapidly in the next ten to 30 minutes, and then more slowly over the following two to 12 hours, nearly reaching but rarely exceeding the pretreatment level. The response to successive injections is frequently better than that to the initial injection.

Treatment of hypertensive emergencies with HYPERSTAT I.V. Injection should be limited to a few days and a regimen of oral antihypertensive medications should be instituted as soon as possible.

With the patient recumbent, the contents of one 20 ml. ampule containing 300 mg. of HYPERSTAT I.V. Injection are administered intravenously in 30 seconds or less. Slow intravenous injection may fail to reduce the blood pressure or may produce an exceedingly short response.

Specific dosage is required in children or in unusually large or small patients. This dosage may be calculated on the basis of 5 mg./kg. body weight (0.3 ml./kg.) (See Warnings).

A second administration of HYPERSTAT (diazoxide) I.V. Injection may be required for a satisfactory reduction in blood pressure, if the first injection fails to give an adequate response within 30 minutes.

Repeated administration of HYPERSTAT I.V. Injection at intervals of four to 24 hours usually will maintain the blood pressure below pretreatment levels until a regimen of oral antihypertensive medication becomes effective. The interval between injections may be adjusted by the duration of the response to each injection. It is usually unnecessary to continue treatment with HYPERSTAT I.V. Injection for more than four to five days.

Following the use of HYPERSTAT I.V. Injection, the blood pressure should be monitored closely until it has stabilized. Thereafter, measurements taken hourly during the balance of the effect will indicate any unusual response. A further decrease in blood pressure at 30 minutes or more after injection should be investigated for causes other than the action of HYPERSTAT I.V. Injection. It is preferable that the patient remain recumbent for half an hour after injection. In ambulatory patients, the blood pressure should be measured with the patient standing before surveillance is ended.

Since repeated administration of HYPERSTAT I.V. Injection can lead to sodium and water retention, administration of a diuretic may be necessary both for maximal blood pressure reduction and to avoid congestive failure.

How Supplied HYPERSTAT I.V. Injection is supplied in a 20 ml. ampule containing diazoxide 300 mg. in a clear, colorless aqueous solution; box of one ampule.

Protect from light and freezing.

Store away from heat.

AUGUST 1973

20 ml.
in 30 seconds or less
for direct action

SWW-4940

Schering

Schering Corporation
Kenilworth, N.J. 07033

Our patient care commitment... yesterday, today and tomorrow.

Yesterday. The Honeywell patient care commitment began more than 15 years ago. We recognized that physiological data systems must consist of more than just good hardware, that our commitment to you and better patient care must be total.

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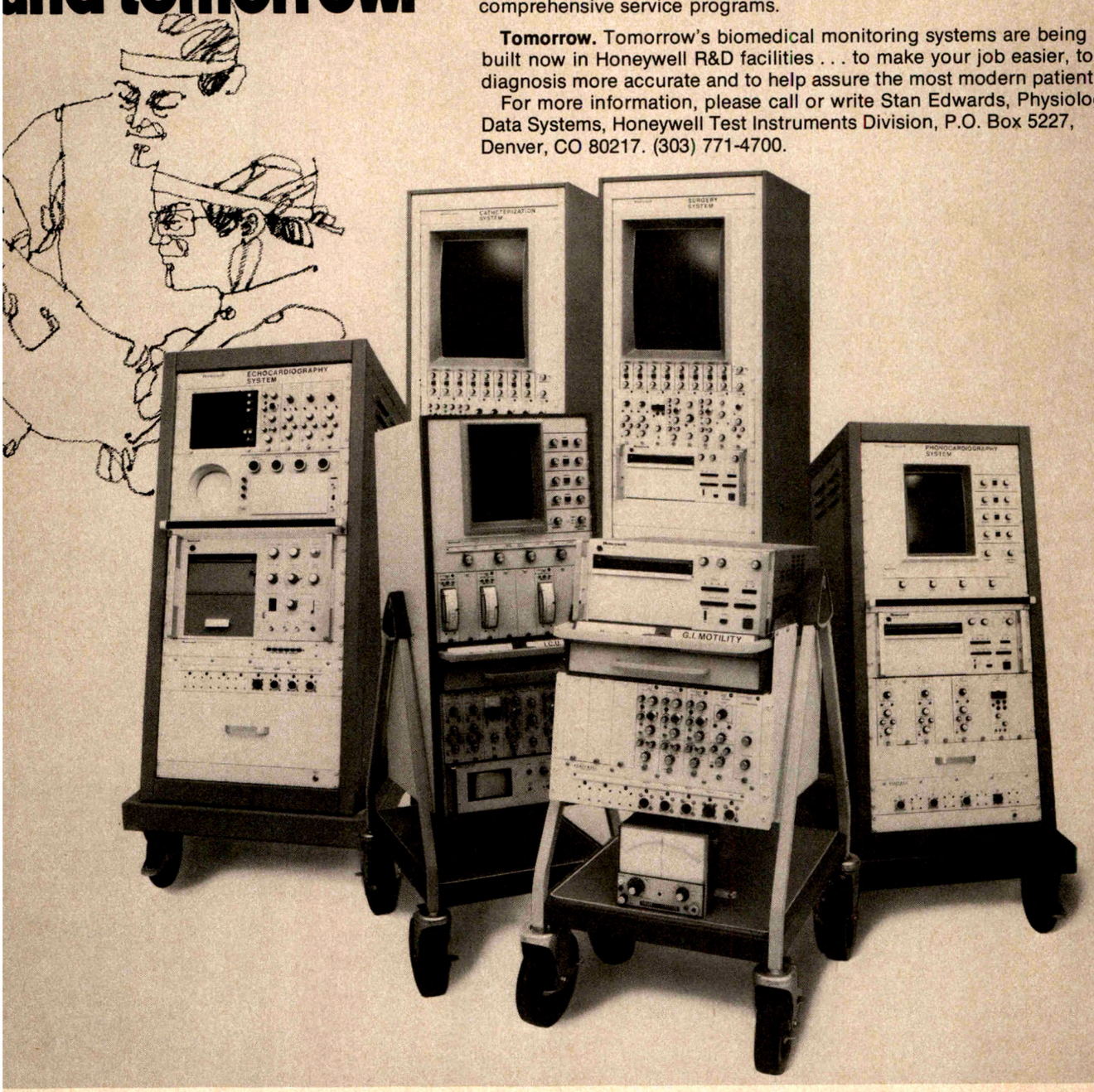

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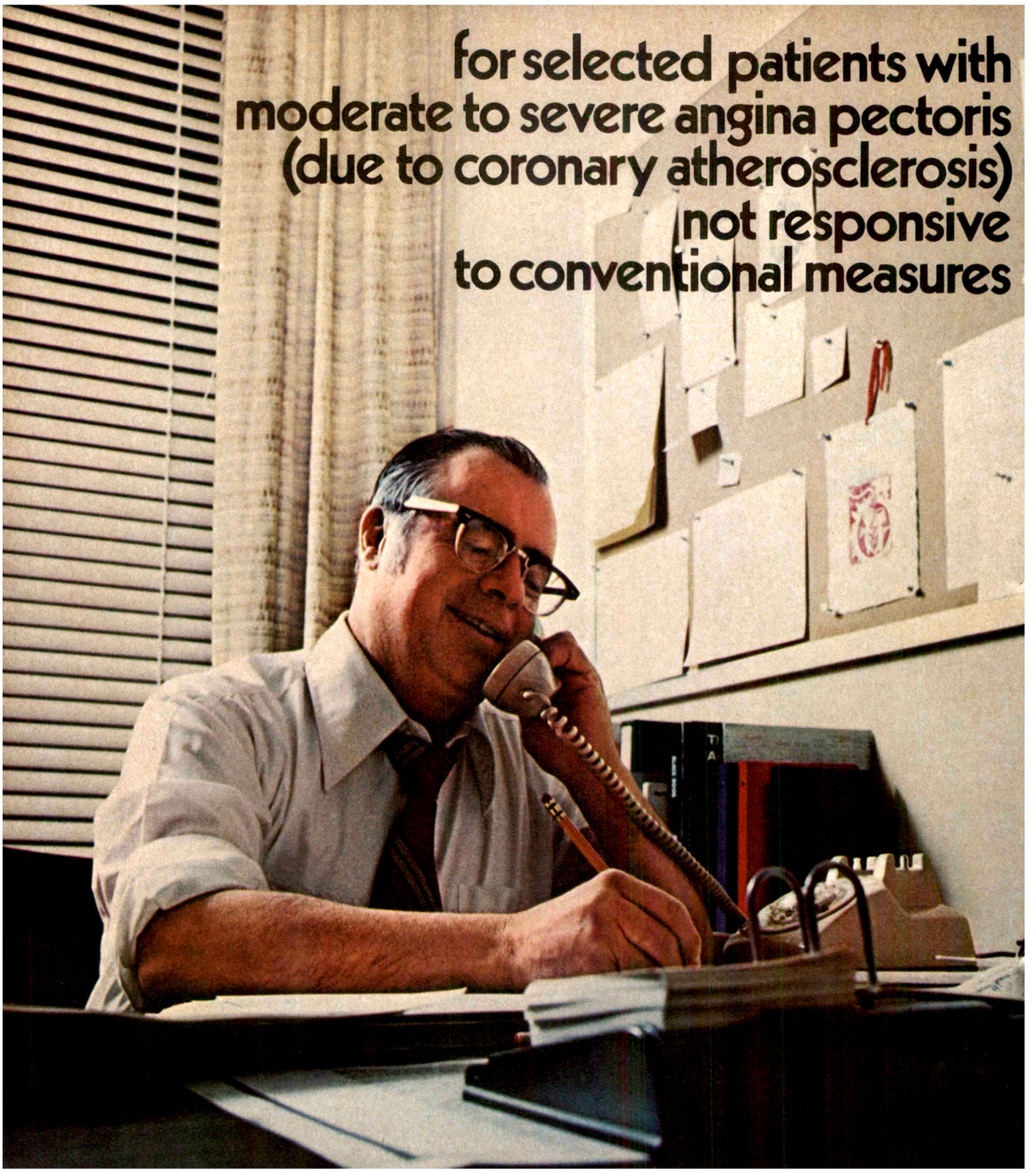

for selected patients with
moderate to severe angina pectoris
(due to coronary atherosclerosis)
not responsive
to conventional measures

Inderal® often enables more activity with less pain

can permit a more normal life

INDERAL (propranolol hydrochloride) often improves exercise tolerance, and thus enables the responsive patient to do more with less pain. When the diagnosis of angina pectoris has been carefully established, and after failure of an adequate trial of such conventional measures as weight control, cessation of smoking, rest, avoidance of precipitating factors, and sublingual nitroglycerin, INDERAL may be added to the regimen of selected patients with moderate to severe angina pectoris. Patients selected to receive INDERAL must not have existing heart failure or bronchial asthma; and all contraindications, warnings, and precautions should be carefully observed (see "Guidelines for using INDERAL" on following page).

INDERAL should not be continued unless there is reduced pain or increased work capacity.

decreases myocardial oxygen demand

When physical effort or other precipitating factors cause excessive catecholamine stimulation of the heart, the demand for oxygen may exceed capacity for delivery of oxygen in a coronary circulation compromised by atherosclerosis. The result—anginal pain.

Thus, in responsive patients, the net effect of INDERAL is to reduce cardiac work (rate × force of contraction) so that oxygen demand can be met more adequately by a reduction of sympathetically induced increases in heart rate, systolic blood pressure and velocity of contraction.

On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to the decreased oxygen requirement.

to reduce pain

Reduction in anginal pain, as indicated either by fewer anginal attacks, more pain-free days, or lowered consumption of nitroglycerin tablets, has been clearly demonstrated in 29 clinical studies.[1-29] One other study reported that propranolol was not effective.[30] The results showed that approximately three-quarters of the patients had less pain and used less nitroglycerin when taking INDERAL than on placebo.

and increase work capacity

In 14 of 17 controlled clinical trials, INDERAL was shown to increase work capacity.[2,8,10,12,13,15,16,18,22,23,25,27,28,31]

In one of these investigations, an eight week double-blind crossover study,[8] the effects of propranolol hydrochloride were evaluated in 19 (18 male, 1 female) patients with rigorously documented angina pectoris of at least six months' duration with a minimum of five episodes per week, and a positive Master 2-step test. "The number of episodes of pain was reduced, nitroglycerin consumption was decreased, and exercise tolerance was increased."

Inderal®

Brand of

propranolol hydrochloride

Ayerst®

Tablets 10 mg., 40 mg. and 80 mg.

(See last two pages of advertisement for prescribing information.)

Guidelines for using Inderal®
(propranolol hydrochloride)

selection of patients

INDERAL is indicated for selected patients with moderate to severe angina pectoris who have failed to respond to an adequate trial of conventional measures, including weight control, cessation of smoking, rest, avoidance of precipitating factors, and sublingual nitroglycerin. INDERAL should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL has a widespread pharmacologic action and therefore a potential for adverse effect. The diagnosis of angina should therefore be more carefully established before instituting INDERAL than may be warranted before beginning conventional therapy. Due consideration must be given to the contraindications and warnings associated with beta-adrenergic blockade.

adequate and individualized dosage

Dosage must be individualized. Starting with 10-20 mg. three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg. per day. The value and safety of dosage exceeding 320 mg. per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

role of congestive heart failure

Inhibition with beta-blockade carries the potential hazard of depressing myocardial contractility and precipitating cardiac failure in patients either with or without a history of cardiac failure. INDERAL is contraindicated in patients with congestive heart failure and heart block unless the failure is secondary to a tachyarrhythmia treatable with INDERAL. (See WARNINGS.)

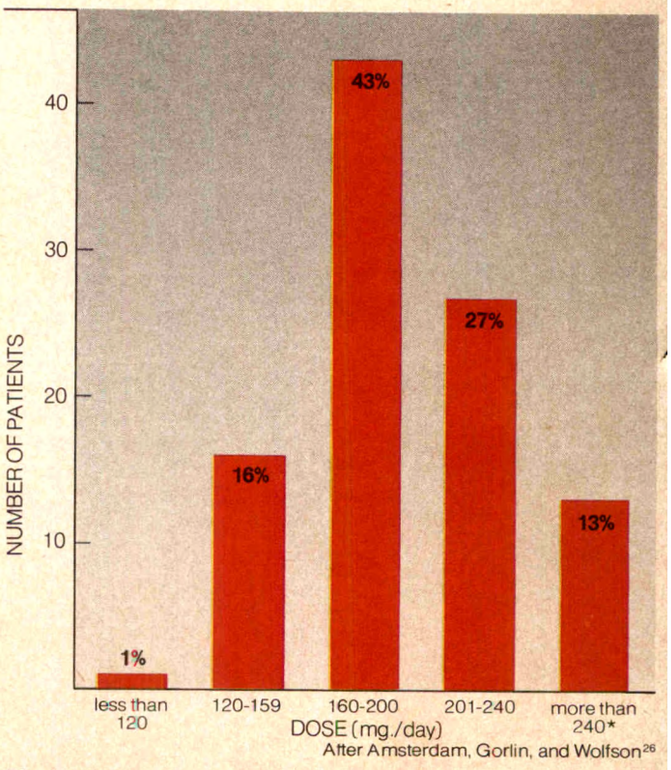
At the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely. If cardiac failure continues, propranolol should be withdrawn, keeping in mind the need to avoid *abrupt* withdrawal unless required by overriding clinical considerations.

avoid abrupt withdrawal of Inderal

There have been reports of exacerbation of angina and of myocardial infarction occurring in angina pectoris patients following *abrupt* discontinuation of INDERAL therapy. The patient should be cautioned against interruption or cessation of therapy without his physician's advice. When discontinuance of chronically administered INDERAL is planned, the dosage should be gradually reduced over a period of weeks and the patient should continue to be carefully monitored.

most patients need about 160mg. a day

DURATION OF THERAPY 29.4 ± 16.5 MONTHS (MEAN ± S.D.).
NUMBER OF PATIENTS: 89



After Amsterdam, Gorlin, and Wolfson[26]

Effective dosage range in 89 patients with angina pectoris who benefited from INDERAL. The largest group reacted well to between 160 and 200 mg. of INDERAL per day.

**The value and safety of daily doses of more than 320 mg. have not been established. See DOSAGE AND ADMINISTRATION and OVERDOSAGE OR EXAGGERATED RESPONSE.*

for selected patients* with moderate to severe angina pectoris where conventional measures have failed

Inderal®

(propranolol hydrochloride)

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BRIEF SUMMARY

(For full prescribing information, see package circular.)

Inderal®

Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support or vital functional balances.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS: *Angina Pectoris due to Coronary Atherosclerosis*

The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients

(Prescribing information continued on following page.)

*See SELECTION OF PATIENTS on opposite page.

with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH CORONARY ARTERY DISEASE AND/OR ANGINA PECTORIS, when discontinuance of chronically administered INDERAL is planned, the dosage should be gradually reduced over a period of several weeks and the patient should continue to be carefully monitored. There have been reports of exacerbation of angina and myocardial infarction occurring following *abrupt* discontinuation of INDERAL therapy.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, non-thrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The oral route of administration is preferred.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 10-20 mg. three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg. per day. The value and safety of dosage exceeding 320 mg. per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL

(propranolol hydrochloride)

TABLETS

No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each tablet contains 80 mg. of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

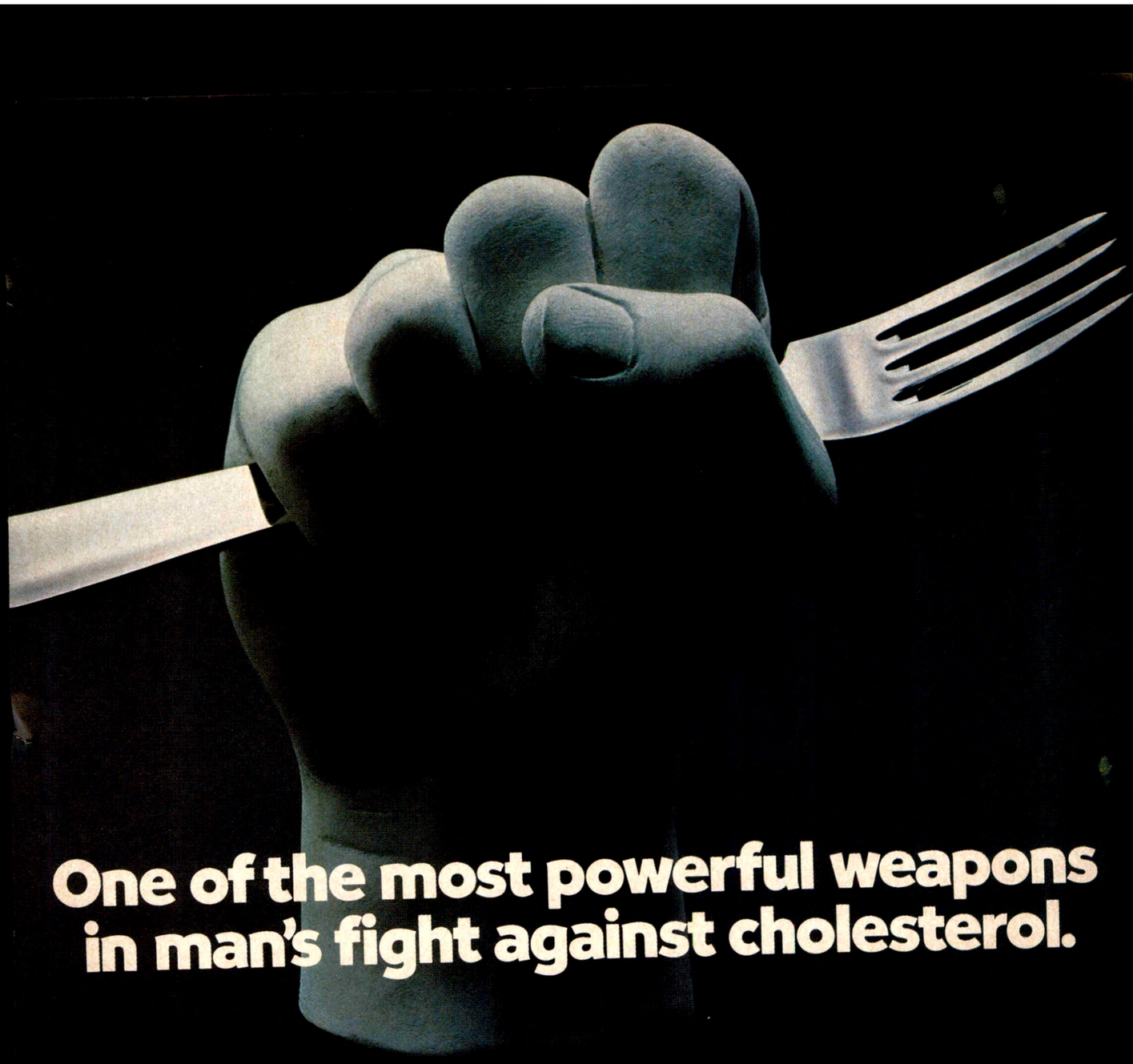
Inderal®

(propranolol hydrochloride)

for selected patients with moderate to severe angina pectoris

Ayerst® AYERST LABORATORIES
NEW YORK, N.Y. 10017

7502



One of the most powerful weapons in man's fight against cholesterol.

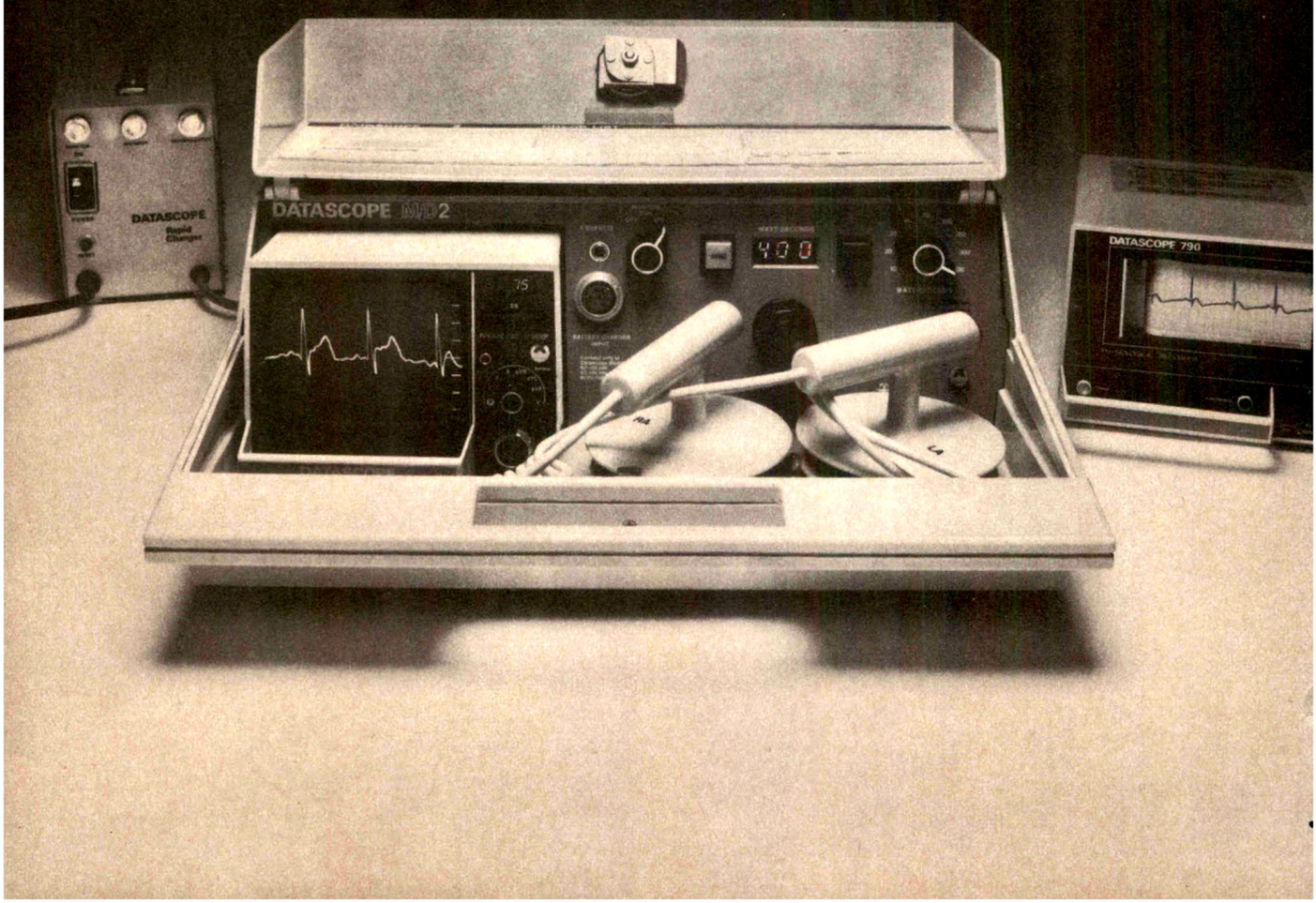
A low saturated fat/low cholesterol diet can be effective, easy to maintain and delicious with the help of Fleischmann's® Margarine and Egg Beaters,™ Fleischmann's cholesterol-free egg substitute.

Of all leading margarines, only Fleischmann's is made from 100% corn oil. And clinical tests show corn oil is unsurpassed in lowering serum cholesterol levels. Fleischmann's Margarine brings that corn oil goodness and delicious taste to your patients' diets. And Egg Beaters, Fleischmann's cholesterol-free egg substitute, lets patients enjoy the taste and nutrition of eggs, but no cholesterol. Yes, Fleischmann's helps a butter-and-egg man enjoy a delicious, sensible diet that's low in cholesterol and saturated fat. We even have free recipe booklets to give patients lots of ideas on sensible eating. To receive your sample copy of "Dietary Control of Cholesterol" and "Cooking with Egg Beaters," write to Fleischmann's, P.O. Box 1538, Elm City, North Carolina 27898. Allow 4-6 weeks for delivery. Offer good only in U.S.A. while supply lasts. Address must include zip code. Void where prohibited.

Fleischmann's makes sensible eating delicious.

Fine products of *Standard Brands*

THE DATASCOPE M/D2 SYSTEM. THE FIRST RESCUE SYSTEM AS FLEXIBLE AS THE PEOPLE WHO USE IT.



If there's one thing you can be sure of in cardiac rescue, it's that you can't be sure of anything.

Every situation, either in the hospital or in the field, presents new problems, and requires new solutions.

At Datascope, we've been in emergency medicine since its inception.

Our equipment has faced just about everything. And from that experience we've put together a system that's prepared to face anything: the M/D2 System.

The M/D2 System is built on one very simple principle. *Every instrument in the system must be independent and not compromised by any other instrument.*

In keeping with this philosophy, our monitor, our defibrillator and our strip-chart recorder each have a separate battery source. One unit never puts a drain on another.

But to see its flexibility, let's take our system apart, instrument by instrument.

OUR MONITOR.

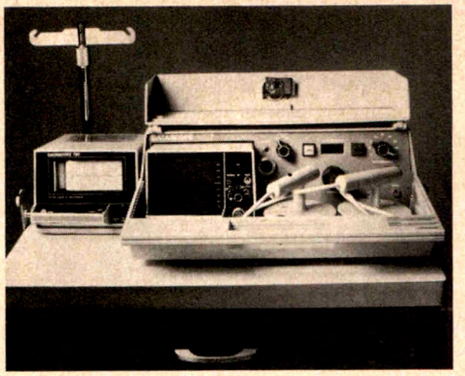
The monitor in the M/D2 System nests inside the defibrillator. You can carry the monitor and defibrillator, use it, and store it as one unit.

But the monitor pulls out* of the M/D2 case and works as a separate unit as well. So it can be placed right on a patient's stretcher in the field. Or put in the most advantageous viewing position at the bedside.

U.S. PATENT 3,865,101

In addition to being so flexible, our monitor outperforms any monitor in emergency medicine.

It has a 5-inch scope with a 8 x 11 cm. viewing area.



It has a memory which provides a bright, non-fade display that's remarkably clear even in strong sunlight.

It has a freeze button which lets you stop the ECG for closer study.

It's the only emergency monitor with a digital heart rate readout. And because the readout is an LED display, you can even read it in the dark.

OUR DEFIBRILLATOR.

Like our monitor, our defibrillator has its own battery-pack.

It's the only defibrillator made that gives you a *digital* energy meter. Which displays both stored energy and the results of delivered energy tests.

The defibrillator is exceptionally safe. A warning tone sounds when the selected energy level is reached.

Energy cannot be delivered unless the push-button switch on each paddle is actuated simultaneously.

The energy within the defibrillator is automatically discharged when the unit is turned off.

For paramedic use, the M/D2 is available completely shielded against RF interference across the entire communications band.

OUR RECORDER.

Our recorder is flexible as well. It's carried separately and powered separately. (For good reason. A recorder powered by a common battery puts an enormous drain on the other instruments in the system.)

Our recorder weights only 11 pounds. And when you're using our monitor outside the M/D2 case, our recorder fits right into the space the monitor vacated. Which allows even easier transport.

OUR RAPID CHARGER.

Although the M/D2 comes with a standard battery recharger, we offer the first rapid recharging unit as part of our system. Our Rapid Charger allows you to defibrillate with just 60 seconds of recharge. And in just 10 minutes it will recharge the defibrillator to at least 60% of total capacity.

THE SYSTEM. IT'S MORE THAN ANY OF ITS PARTS.

Three independent units. Three independent battery-packs. And a Rapid Charger. They work together, or apart. They give you more ability to react than any single unit ever could.

For more information on the M/D2 System, write: Datascope Corp., 580 Winters Avenue, Paramus, N.J. 07652.

THE DATASCOPE M/D2

The art of antianginal therapy

For centuries, treating the heart's ills has been the subtlest of arts. Even today, evaluating a drug for chronic angina pectoris involves the art of medicine as well as its science.

During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Give enough, long enough—The recommended dosage: 50 mg t.i.d. at least one hour before meals for several weeks or longer.

Persantine® Tablets of 25 mg
dipyridamole

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

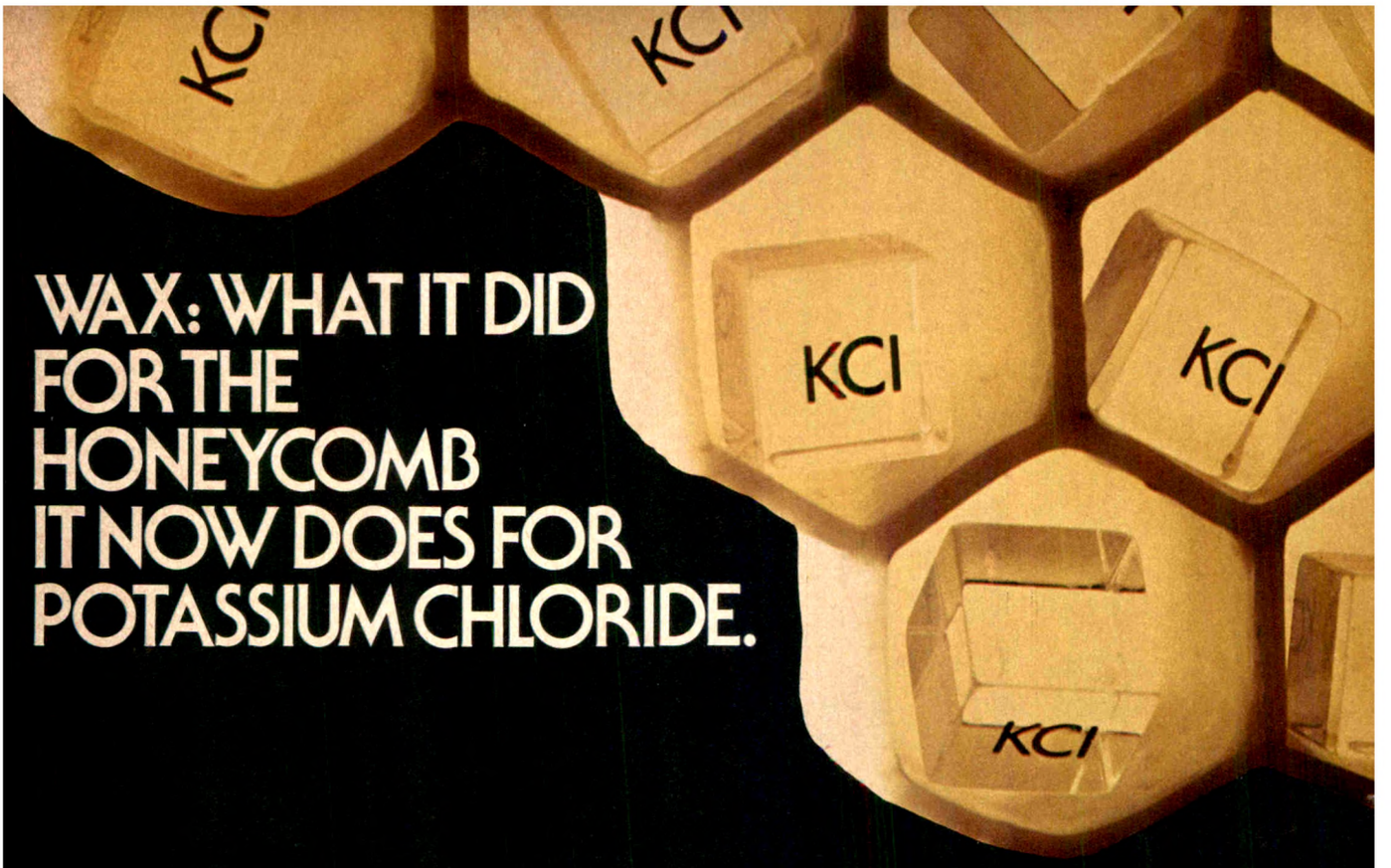
For complete details, please see the full prescribing information.

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Elmsford, N.Y. 10523

One of a series of paintings of the heart in the style of well-known artists.

The Heart . . . in the style of Vincent van Gogh (1853-1890)

He created paintings and drawings of uncommon luminosity and dynamism. His works, marked by profound emotions and a stirring power of expression, had a decisive influence on all of modern painting.



WAX: WHAT IT DID FOR THE HONEYCOMB IT NOW DOES FOR POTASSIUM CHLORIDE.

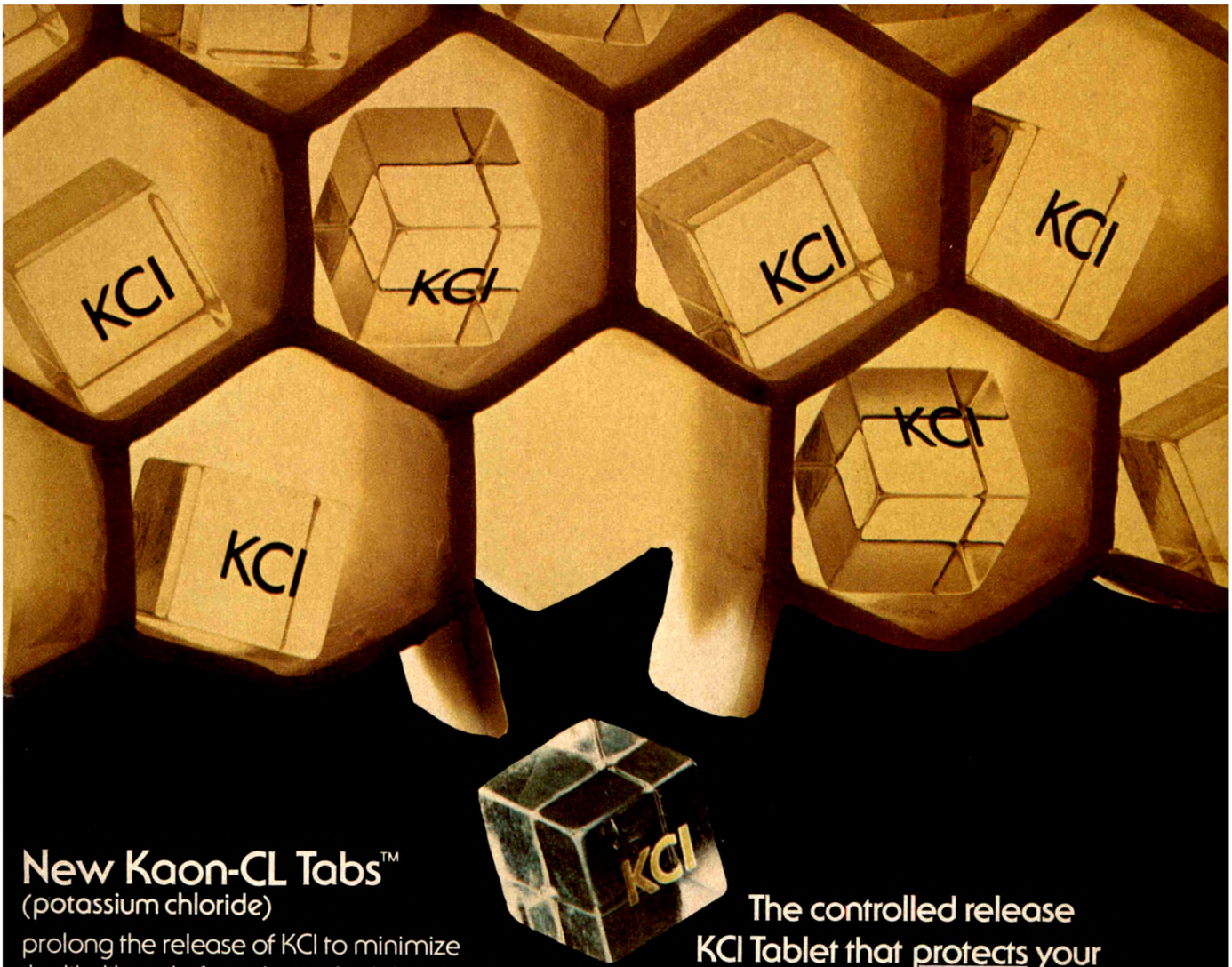
WARREN-TEED® ANNOUNCES

NEW KAON-CL TABS™

(potassium chloride)

CONTROLLED RELEASE TABLETS

– Potassium chloride imbedded in a wax matrix to provide controlled release, thus minimizing possible high local concentration of potassium ion near the bowel wall. The newest idea in potassium chloride supplements is as old as the beehive. Wax... provides an effective vehicle to imbed KCl



New Kaon-CL Tabs™
(potassium chloride)

prolong the release of KCl to minimize the likelihood of producing high localized concentrations of potassium within the G.I. tract...

- protect your patient from the risk of hypokalemia or digitalis intoxication due to potassium depletion that diet alone cannot correct...
- promote adherence to medication schedule by relieving the patient of the inconvenience of liquids...

Three-way convenience for your patients on KCl Supplements...

- because there's no palatability problem
- because there's no dilution problem
- because tablets are physically easier to carry—and to take—than liquids... an especially welcome advantage away from home—encouraging adherence to the prescribed regimen

The controlled release KCl Tablet that protects your patients on diuretics or digitalis

- against hypokalemia due to potassium depletion that cannot be adequately replaced by diet alone
- against the inconvenience of—and often confusion over—dilution of liquid supplements
- from taste-fatigue associated with liquids

Dosage: Prophylactic: 20 mEq. daily (1 tab T.I.D.)
Therapeutic: 40-100 mEq. daily
See following page for brief summary.

WARREN-TEED
PHARMACEUTICALS INCORPORATED
SUBSIDIARY OF ROHM AND HAAS COMPANY

Warren-Teed®
KAON-CL TABS™
(Potassium Chloride)
CONTROLLED RELEASE TABLETS

Description: Kaon-CL Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg. potassium chloride (equivalent to 6.67 mEq. potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: Kaon-CL Tabs is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. Kaon-CL Tabs is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

Warnings: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-CL Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric coated potassium chloride tablets (40-50 per 100,000 patient-years), a few cases associated with wax-matrix tablets have been reported. These data are from foreign marketing experience. Kaon-CL Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia, in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Dosage and Administration: Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq. per day for the prevention of hypokalemia to 40-100 mEq. per day or more for the treatment of potassium depletion.

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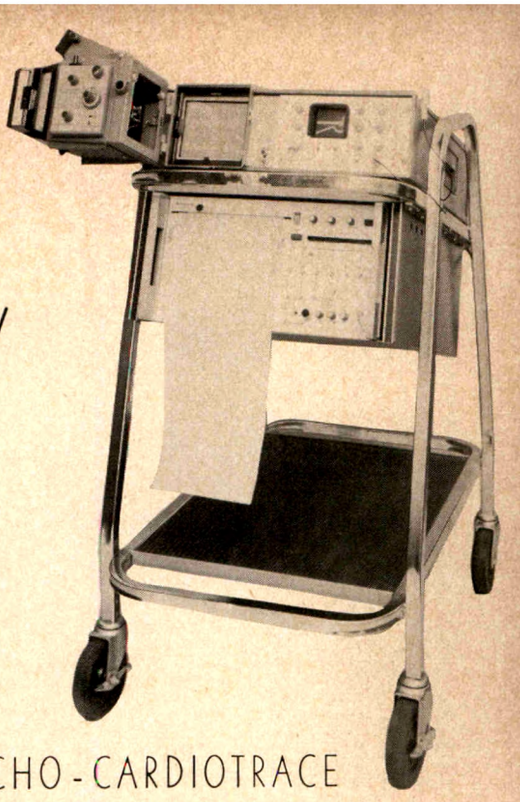

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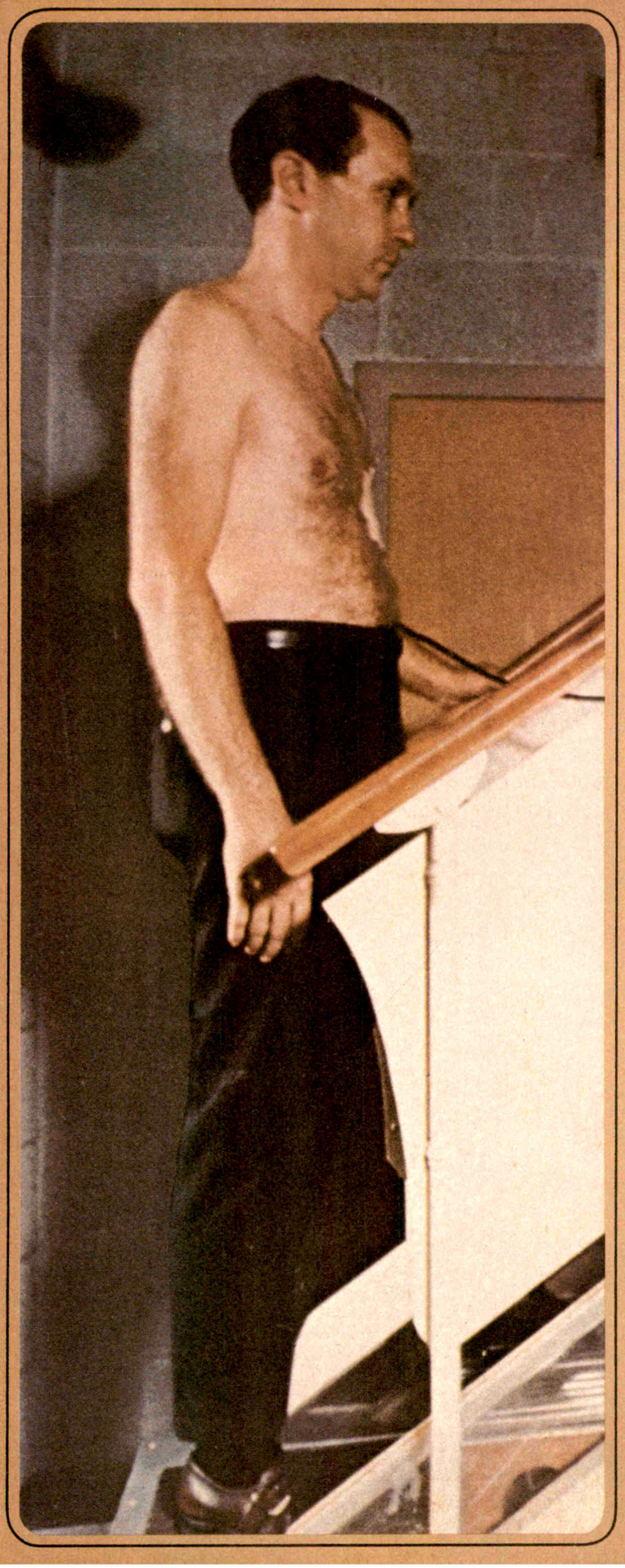

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CLINICAL STUDIES

Left Main Coronary Arterial Obstruction: Long-Term Follow-Up of 141 Nonsurgical Cases

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The prognosis of 141 patients with obstructive left main coronary artery disease was studied. The patients were followed up for 5 to 10 years from the date of coronary arteriography. The 5 year cardiac mortality rate was 51 percent. During the first 3 years after diagnosis, the mortality rate was especially high, 21.9, 34.7 and 43 percent, respectively. Among patients who died in the 1st year after diagnosis, evidence of left ventricular hypertrophy or conduction delay in the electrocardiogram and multiple vessel involvement indicated poor prognosis. Severe angina pectoris, evidence of congestive heart failure and generalized decrease in left ventricular contractility increased the 5 year mortality rate. More than 97 percent of the total patient population had additional lesions elsewhere in the coronary arteries.

The left main coronary artery supplies branches to most of the left ventricle. An obstructive lesion involving this vessel suggests a poor prognosis. Recent studies[1–3] have tended to support the impression that patients with this lesion constitute a high risk group. A long-term progress study of a large population of patients who did not have surgical intervention is not available.

Selection of Patients and Methods

Patients who had coronary arteriography from January 1961 through December 1966 were selected for this study. Those included had at least 50 percent narrowing of the left main coronary artery and had no coronary surgery within 5 years from the date of coronary arteriography. Patients with congenital or rheumatic heart disease were excluded. The objective was to obtain a minimal follow-up period of 5 years for all patients who had not undergone surgery during that time. One hundred forty-one consecutive patients fulfilled the selection criteria; all were successfully followed up for a minimum of 5 years, and 96 percent were followed up for 6 years. These patients constituted 6 percent of the subjects with obstructive disease by coronary arteriography.

All patient data were coded before follow-up information was collected. Clinical symptoms were classified according to previously established criteria.[4] A diagnosis of hypertension was made if at the time of admission for coronary arteriography the systolic blood pressure was 150 mm Hg or more, or

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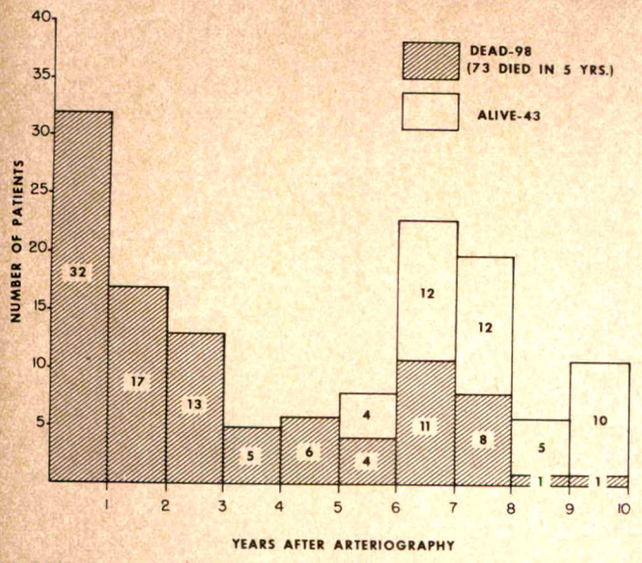

FIGURE 1. Duration of observation after arteriography in 141 patients. The date of arteriography is used as the zero point in time. Sixty-eight patients were alive after 5 years. The difference in duration of follow-up of those alive after 5 years is due to the difference in dates of arteriography.

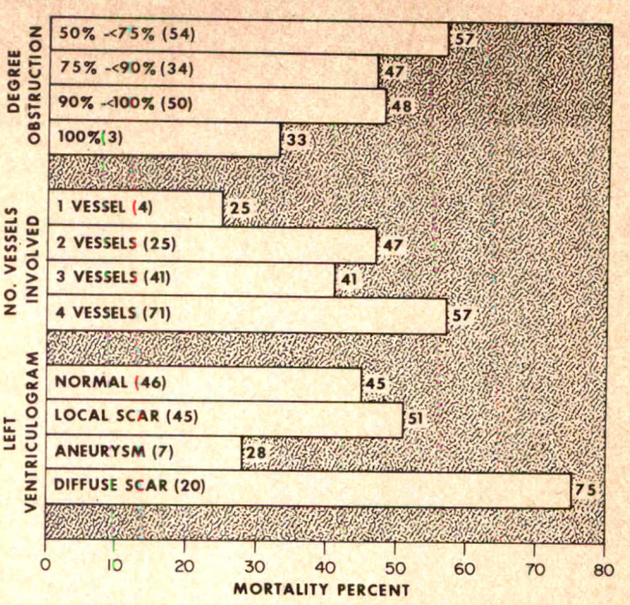

FIGURE 2. Five year cardiac mortality rates in relation to cardiac catheterization findings. The rates are higher in patients with four vessel disease and in those with generalized decreased contractility of the left ventricle.

TABLE I

Relation Between 5 Year Cardiac Mortality Rate and Data from the Coronary Arteriogram and Left Ventriculogram*

	Left Ventriculogram			
Coronary Arteriogram	Normal	Localized Scar	Aneurysm	Diffuse Scar
1 vessel involvement (left main coronary)	50 (2)	0	0	0
2 vessel involvement	50 (10)	62 (8)	0 (2)	33 (3)
3 vessel involvement	25 (12)	38 (13)	50 (2)	83 (6)
4 vessel involvement	50 (22)	48 (25)	33 (3)	90 (11)

*Data expressed as percent with total number of cases in each category in parentheses. Twenty-two patients without a left ventriculogram were not included in the calculations.

the diastolic pressure was 100 mm Hg or more. The obstruction in the coronary arteries was classified as 50 to less than 75 percent narrowing of lumen diameter, 75 to less than 90 percent narrowing, 90 percent narrowing to almost total obstruction and total obstruction. The presence of demonstrable collateral formation from either a right to left or left to right direction was noted. Follow-up data were obtained by questionnaires and telephone interviews. The principal sources of information were attending physicians, the patients, their relatives and former employers.

The 5 year mortality rate for various categories was calculated by the direct method. The survival curve was constructed by actuarial method[5] and analysis of data was performed manually.

Results

Figure 1 shows the duration of observation of the 141 patients after arteriography. Ninety-eight pa-

TABLE II

Obstruction of the Left Main Coronary Artery (141 Patients)

	Deaths per Year after Coronary Arteriography*											5 Year Cardiac Mortality Rate (%)
Obstruction	0-1 Year	1-2 Years	2-3 Years	3-4 Years	4-5 Years	5-6 Years	6-7 Years	7-8 Years	8-9 Years	9-10 Years	Survivors	Total
50—<75%	10	11	3	3	4	2 (1)	3	2 (1)	...	1	15	54	57.4
75—<90%	5 (1)†	5	4‡	2	1	1	3 (1)	3 (1)	1	...	9	34	47
90%—subtotal	16§	1	6	...	1	1	4	3	...	...	18	50	48
100%	1	...	...	...	...	...	1	...	...	...	1	3	33
Total	32 (1)	17	13	5	6	4 (1)	11 (1)	8 (2)	1	1	43	141	51

* Total number of deaths, noncardiac deaths in parentheses.
† One died from stroke.
‡ One died after heart transplantation.
§ Three died on day of arteriography (one from myocardial infarction, one from coronary dissection, one from arrhythmia).

tients died in the follow-up period and 43 survived. The patients with longer follow-up periods had arteriography performed at earlier dates.

Clinical features: The clinical data on those who died within 5 years and on those who survived were compared. The ages ranged from 26 to 63 years (mean 53 years) in 7 women and from 32 to 72 years (mean 52 years) in 134 men. The ratio of slightly greater than 19 men to 1 woman is higher than the ratio of 8.2 men to each woman in a previous progress study[3] of unselected patients. Hypertension was noted in 34 percent of the patients and, although the number of cases was small, there was no apparent difference between the incidence of hypertension in survivors and nonsurvivors. The serum cholesterol value at the time of admission for coronary arteriography was also not significantly different in the two groups.

Mortality and arteriographic findings: The 5 year cardiac mortality rate correlated with the cardiac catheterization findings (Fig. 2). The degree of obstruction of the left main trunk did not appear to affect the 5 year mortality rate. Since more than 97 percent of the patients had multiple arterial involvement, the mortality in patients with lesser degrees of narrowing could be explained on this basis. Because only four patients had isolated left main coronary artery disease, comparison of their data with those of patients who have additional lesions is difficult. Diffuse involvement, as exemplified by four vessel disease, appears to have a high mortality rate. Patients with generalized decreased contractility of the left ventricle have a poor prognosis (75 percent 5 year mortality rate). The presence of a localized abnormality in contractility did not make a significant difference in mortality when data in affected patients were compared with those in patients with a normal left ventriculogram.

When the number of vessels involved and the left ventriculogram were correlated with the 5 year mortality rate, the rate was highest in the category with multiple vessel involvement combined with diffuse decrease in contractility (85 and 90 percent mortality rate in three and four vessel involvement, respectively, Table I). Left ventriculograms were not made in 22 patients whose data were therefore not included in the correlation. Because the value of left ventriculography was not appreciated at the time, it was not routinely performed in our early experience. Intercoronary collateral formation was present in 89 patients (63 percent). Those who died within 5 years tended to have more frequent demonstrable collateral vessels (right to left as well as left to right), but the difference was insignificant (49 to 73 versus 40 to 68).

The 5 year cardiac mortality rate for the whole group of patients was 51 percent (Table II). There were only 5 noncardiac deaths among the 98 deaths in the follow-up period. Thirty-one cardiac deaths, including three at catheterization, occurred in the 1st year after arteriography (43 percent of the 5 year cardiac mortality rate). Of 53 patients with severe left main coronary arterial stenosis (75 percent narrowing to total occlusion), 52.8 percent (28 patients) survived more than 5 years; 2 of these patients subsequently received coronary bypass grafts.

Factors influencing 5 year survival: Various factors were analyzed (Table III) to determine how those who survived more than 5 years differed at the time of catheterization from those who died in less than 5 years. In addition, because of the high mortal-

TABLE III
Comparison of Patients Who Died Within 1 Year and Between 1 and 5 Years, and Those Who Survived More Than 5 Years

	Died Within 1 Year	Died Between 1 and 5 Years*	Alive at 5 Years
Number of patients	31	41	68
Symptoms†			
Angina class 2	4	4	24
Angina class 3	4	5	6
Rest pain/coronary failure pain‡	15	26	32
Atypical pain	3	0	4
Congestive heart failure	5	6	2
Electrocardiogram			
Normal†	9	13	33
Repolarization disturbances	6	9	17
Myocardial infarction	8	17	15
Left ventricular hypertrophy or conduction delay†	8§	2	3
Coronary arterial narrowing (%)			
50—<75	14	17	23
75—<90	3	13	18
90—<100	13	11	26
100	1	1	1
Number of vessels involved			
1 (left main)	1	0	2
2	6	6	13
3	10	7	24
4	14§	28	29
Left ventriculogram			
Normal	11	10	25
Local scar	9	14	22
Aneurysm	1	1	5
Diffuse impairment†	7	8	5

*One patient who died within 5 years of noncardiac causes is not included in the analysis.

†Statistically significant difference between those who survived 5 years and those who died.

‡Coronary failure pain = pain lasting more than 15 minutes without evidence of myocardial infarction.

§Statistically significant difference between those who died and those who survived (see text).

ity rate during the 1st year, those who died within 1 year were also compared with those who died after the 1st year but within 5 years of arteriography. Evidence of left ventricular hypertrophy or conduction delay in the electrocardiogram and four vessel arterial involvement were the only significant factors in the early mortality data. Comparison of those who died in the 5 year follow-up period with those who survived revealed significant differences in the severity of symptoms (angina pectoris), clear evidence of congestive heart failure on examination or a history strongly suggestive of it in the recent past, normal electrocardiogram or evidence of left ventricular hypertrophy or conduction delay, four vessel involvement and generalized decreased contractility observed in the left ventriculogram.

The survival curves of patients with left main coronary arterial obstruction and those with three vessel disease without involvement of the left main trunk as reported by Bruschke et al.[3] are compared in Figure 3. The curve in patients with left main coronary disease is slightly lower in the first 3 years. The 5 year mortality data are similar in both groups when correction for noncardiac deaths is made for patients with three vessel disease. The survival curves of the two subgroups are significantly lower than that of the unselected population with coronary disease.

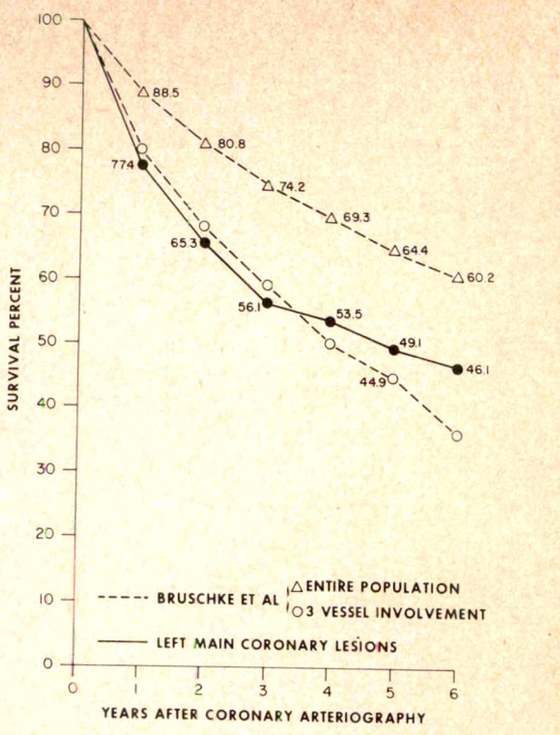

FIGURE 3. Survival curves of patients with left main coronary arterial obstruction and in the series of cases reported by Bruschke et al.[3] Patients with left main coronary arterial lesions were not included in the curve for three vessel involvement.

Discussion

At the time coronary arteriography was performed in these patients, the coronary bypass grafting technique was not available. Consequently, patients with left main coronary arterial obstruction were not treated surgically except for a few attempts at procedures, coronary ostial dilation and direct patch grafting, that had a high surgical mortality rate.[6] The prognosis of this group of patients not operated on could be studied with little bias from surgical selection.

From our study we conclude that the prognosis of patients with left main coronary stenosis is poor, particularly in the first 3 years after diagnosis. Comparison with studies reported by other investigators[1,2] is difficult because of their small series and short period of follow-up. However, the published figure[1] of a 50 percent mortality rate with an average follow-up of 25 months is quite high. Bruschke et al.,[3] from the Cleveland Clinic, reported on 37 patients and their 5 year mortality rate of 56.8 percent is closer to our figure of 51 percent.

The three cardiac catheterization deaths (2.1 percent mortality rate) in this report occurred before 1967, and this figure is relatively high since the overall mortality rate for coronary arteriography in our laboratory was less than 0.1 percent at that time. It probably reflects a combination of insufficient experience with this type of lesion and the lack of an effective surgical procedure to deal with it. Opacification of the left coronary ostium, performed cautiously in the left anterior oblique projection with a small amount of contrast medium, should precede selective left coronary arteriography. When a left main coronary lesion is revealed by this "test dose," left coronary arteriography is carried out expeditiously with the catheter tip positioned at or just inside the left ostium. The number of injections of contrast medium is kept to an adequate minimum, enough to visualize the two main branches of the left coronary artery. The capability of performing immediate revascularization with bypass grafts, when required, must be available.

Among patients with obstructive coronary artery disease the subgroups having left main trunk obstruction or multiple vessel involvement have the worst prognosis. In those with left main trunk obstruction and multiple vessel obstruction, surgery seems particularly indicated. Evidence of left ventricular hypertrophy or conduction delay in the electrocardiogram and of severe diffuse impairment of contractility in the left ventriculogram are additional factors that worsen the prognosis.

Although the arteriographic and left ventriculographic findings have predictive value, a number of patients with severe obstructive disease in the left main coronary artery and a few with a poorly contractile left ventricle or a combination of these lesions survive many years. They are the exceptions, but they illustrate the varied and complicated course of patients with this disease.

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Left Main Coronary Artery Disease

Risks of Angiography, Importance of Coexisting Disease of Other Coronary Arteries and Effects of Revascularization

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To elucidate the determinants of the poor prognosis of patients with left main coronary artery disease and to assess the efficacy of diagnostic and therapeutic interventions the angiographic features and clinical course of 58 patients with left main coronary artery disease studied between September 1967 and June 1974 were analyzed. Eighty-three coronary arteriograms were obtained in these 58 patients using the Judkins technique; there were no immediate complications although one patient died 3 days after study. Previously cited predictors of left main coronary artery disease such as calcification of the left main coronary artery, unstable or nonexertional angina and marked S-T segment depression with exercise were found in a minority of patients; thus, the presence of the disease could not reliably be predicted before arteriographic study. Coexisting disease was found in either two or three other coronary arteries in 46 of 58 patients; only 2 patients had isolated left main coronary artery disease.

Because the criteria for operability have changed in recent years, operability in each case was reassessed by two investigators using current criteria without knowledge of the treatment actually given or its outcome. The condition of 10 of 58 patients was judged inoperable in retrospect because of severe coexisting distal coronary artery disease (8 patients) or ventricular dysfunction (2 patients). Of 19 patients whose condition was judged operable in retrospect but who were treated without surgery, 9 died, 8 within 18 months; 10 have survived 12 to 83 months. Another 27 patients with a condition judged operable in retrospect had received saphenous vein bypass grafts. In this group, there were four operative and three late deaths. The severity of angina decreased in survivors treated surgically but was unchanged in survivors treated without surgery. The improvement in survival rates of surgically treated patients was not statistically significant.

The data indicate that coronary arteriography can be performed at low risk with the Judkins technique even though preangiographic prediction of left main coronary artery disease is unreliable. Coexisting disease in other major coronary arteries is an important determinant of the poor prognosis of patients with left main coronary artery disease and precludes surgery in 13 percent. Isolated left main coronary artery disease is uncommon. Surgical therapy relieves symptoms more effectively than nonsurgical therapy.

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Recent reports have described the clinical presentation, the poor prognosis and the increased risks of coronary arteriography and surgery in patients with left main coronary artery disease.[1–4] This review of 58 patients examines, in particular, the suitability of the Judkins technique[5] for the coronary arteriographic examination of patients with left main coronary artery disease, arteriographic findings relating to the poor prognosis of such patients, reliability of clinical indexes for the preangiographic prediction of the disease and the impact of coronary arterial surgery.

Materials and Methods

A review of the 2,450 coronary arteriograms obtained between September 1967 and June 1974 at the University of Oregon Medical School revealed 58 patients with 50 percent or greater reduction in luminal diameter of the left main coronary artery. A 50 percent reduction of luminal diameter corresponds to a 75 percent reduction of cross-sectional area and produces a significant reduction of blood flow.[6,7] The Judkins technique was used in all studies.[5,8] Twenty-two patients had two angiographic studies each and one patient had four studies. Of these 25 follow-up studies, 6 were performed without intervening surgery at an average interval of 27 months (range 6 to 66 months) and 19 at an average interval of 9 months postoperatively. Two patients with less than 50 percent narrowing on an initial investigation were entered into the study only when 50 percent narrowing of the left main coronary artery was demonstrated in a later investigation.

The degree, type and location of the left main coronary arterial lesion and the severity and location of other coronary artery disease were assessed. Left ventricular cineangiography and pressure were used to evaluate ventricular function. The presence or absence of left main coronary arterial calcification, best identified fluoroscopically, was noted.

Because criteria for operability have changed in recent years, particularly with the advent of saphenous vein bypass grafting, the suitability of each of the 58 patients for saphenous vein bypass grafting was reassessed by two investigators using current criteria. These criteria, which require assessment of the morphologic features of distal vessels, filling patterns, branch disease, runoff capacity and ventricular function, have been described previously.[9] The retrospective determination of operability was made without knowledge of the therapy given or its outcome.

Hospital records, data on outpatient clinic examinations, records of Bureaus of Vital Statistics and interviews with patients, their relatives and referring physicians were used to determine the clinical course of the patients after angiography and surgery. The presence or absence of hypertension, diabetes mellitus, lipid abnormalities or history of prior myocardial infarction was noted. Angina at the time of angiography and at the present time was classified as mild (occurring less than once daily), moderate (occurring several times daily), severe (frequent episodes occurring with mild exertion and at rest in a stable pattern) or unstable (recurrent angina at rest persisting after admission to the hospital with transient ST-T wave electrocardiographic changes).

Electrocardiograms were examined for evidence of transmural infarction, ischemia or nonspecific abnormalities. Stress electrocardiography was performed in 19 patients using supine bicycle exercise with continuous electrocardiographic monitoring.[10]

Survival rates in surgically and nonsurgically treated patients were determined by actuarial method.[11] Standard errors of survival estimates were determined by the Greenwood formula,[12] and the two patient groups were compared using a normal distribution test.[12]

Results

Clinical Features

Angina was severe in 20 patients, unstable in 6, moderate in 24, mild in 5 and absent in 3. The three patients without angina had coronary arteriography in the course of evaluations for valvular or myocardial disease. Although 14 patients gave a history of myocardial infarction, only 7 had evidence for it in their current electrocardiograms. Four additional patients had electrocardiographic evidence of transmural infarction without a clinical history of infarction. Sixteen patients were hypertensive and 6 diabetic; 23 of 40 patients tested had elevations of serum cholesterol and triglyceride levels.

Electrocardiograms were normal in 12 patients and revealed left ventricular hypertrophy in 11, prior myocardial infarction in 12, ischemic ST-T wave changes in 6 and nonspecific abnormalities in 18. Stress electrocardiography was positive in 14 of 19 patients; only 2 of the 19 had S-T segment depression of more than 2 mm.

Of 58 patients, 26 had 50 to 70 percent stenosis and 32 had 71 to 95 percent stenosis of the left main coronary artery. Fifty-six patients had coexisting disease of other major coronary arteries. Twenty-eight had coexisting disease in three other vessels, 18 in two other vessels and 10 in one other vessel. Only two patients had isolated disease of the left main coronary artery. Thirty-six patients had associated disease of the left anterior descending coronary artery, 40 associated disease of the left circumflex coronary artery and 48 associated disease of the right coronary artery. Only six patients had no associated disease of either the left anterior descending or the circumflex coronary artery.

There were no deaths or other major complications during angiography. One patient had ventricular fi

TABLE I

Extent of Distal Disease in Various Subgroups

Group	Number of Associated Major Coronary Vessels Significantly Narrowed				
	3	2	1	0	Total
Nonsurgically treated					
Condition operable, in retrospect					
Survivors	5	3	1	1	10
Nonsurvivors	6	2	1	...	9
Condition inoperable, in retrospect					
Survivors	...	1	...	1	2
Nonsurvivors	4	1	...	...	5
Total	15	7	2	2	26
Surgically treated					
Saphenous vein bypass grafting					
Survivors	10*	3	7	...	20
Nonsurvivors	2	5	...	...	7
Internal mammary implant					
Survivors	2	...	...	...	2
Nonsurvivors	...	3	1	...	4
Total	14	11	8	...	33

* One patient in this group is also included in the group with internal mammary artery implantation.

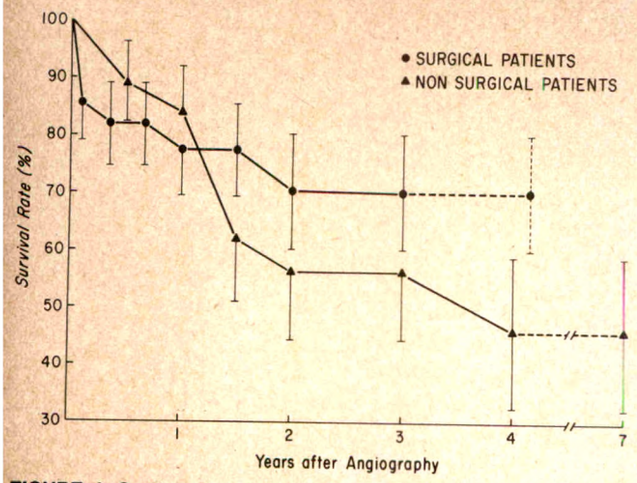

FIGURE 1. Survival curves determined by the actuarial method are shown for the nonsurgically treated patients whose condition was judged operable by current criteria and for patients treated surgically with saphenous vein bypass grafting. The difference in survival rates is not statistically significant. Vertical bars indicate standard error.

brillation 6 hours after angiography and was resuscitated, but died 3 days later of recurrent ventricular arrhythmias. No evidence of myocardial infarction was found at autopsy.

The condition of 10 patients (17 percent) was judged inoperable, in 2 (4 percent) because of ventricular dysfunction (left ventricular end-diastolic pressure greater than 25 mm Hg and ejection fraction less than 0.30) and in 8 (13 percent) because the distal vessels were considered unsuitable for placement of a vein graft.

Follow-Up of Nonsurgically Treated Patients

Surgery was not performed in 26 patients for various reasons, including patient refusal, left ventricular dysfunction and coronary arterial anatomy unsuitable for surgery. One of these patients was lost to follow-up study after 18 months. The frequency of associated disease in these 24 patients is shown in Table I. By current criteria, the condition of seven of these patients was considered inoperable and that of 19 operable. Of the former, five (71 percent) died 3 days to 18 months after angiography (mean survival 6 months). The remaining two are alive after 17 months of observation.

The condition of 19 patients was judged operable by current criteria but they were treated without surgery. Nine of these patients died 1 to 39 months after angiography (average 14 months). One of these nine patients had been accepted for surgery but elected to delay the procedure for a month and died suddenly with ventricular fibrillation. Ten patients are still alive after a period of observation averaging 48 months (range 12 to 83 months). Figure 1 shows the survival curve for these patients. The number of patients at risk and of those surviving at various intervals is shown in Table II. Figure 2 shows the severity of angina of survivors at the time of angiography and currently.

TABLE II

Interval Survival Data For Surgically and Nonsurgically Treated Patients

Surgically Treated Patients*								
Months postoperative (no.)	1	4	8	12	18	24	36	56
Patients at risk (no.)	28	24	23	21	16	11	9	6
Survivors (no.)	24	23	23	20	16	10	9	6
Nonsurgically Treated Patients								
Months after arteriography (no.)	6	12	18	24	36	48	84	
Patients at risk (no.)	19	17	16	11	8	6	4	
Survivors (no.)	17	16	12	9	8	5	4	

* All patients except one were operated on within 1 month of coronary arteriography.

Follow-up of Surgically Treated Patients

Thirty-two patients were treated surgically. Internal mammary arterial implants were performed in 6 of these 32 patients before 1969; there were three operative deaths and one late death 33 months after the procedure. In one of the six, intractable angina recurred and saphenous vein bypass grafting was performed with symptomatic benefit. Three patients whose condition was judged inoperable by current criteria received internal mammary arterial implants. Two of these patients died in the intraoperative period; the third patient is alive nearly 7 years postoperatively.

Twenty-seven patients, one of whom had previously received an internal mammary arterial implant, were treated with saphenous vein bypass grafting. One of the 27 was reoperated on 24 months later when angina recurred and angiography demonstrated extension of disease. There were four operative deaths (14 percent) in the course of the 28 operations; three late deaths were caused by digitalis intoxication, acute myocardial infarction and congestive heart failure, respectively. The suitability of the patient in the latter case for saphenous vein bypass grafting is questionable retrospectively because his ejection fraction was only 0.29. He had no angina after operation but continued to be severely limited by symptoms of heart failure until the time of death. A total of 40 grafts were performed in the 18 patients who had postoperative angiography. Thirty-two (80 percent) of 40 grafts were patent.

Figure 1 shows the actuarially determined survival estimates, and Table I the extent of coexisting disease in these surgically treated patients. All 20 surviving patients experienced reduction in the severity of angina, and 13 of these survivors are angina-free. The functional state of this group of patients before surgery and at present is shown in Figure 2. The surgically and nonsurgically treated groups were similar with respect to frequency of prior myocardial infarction, incidence of hypertension, diabetes mellitus and lipid abnormalities, severity of left main coronary arterial stenosis, extent of distal vessel involvement and

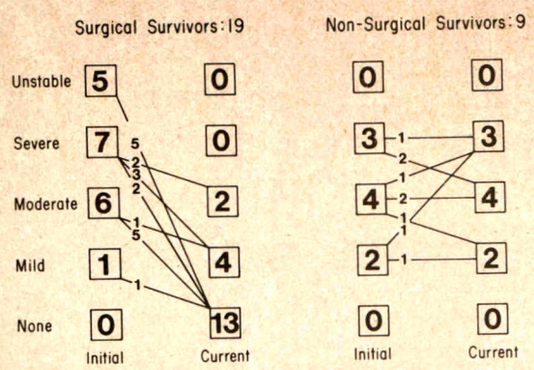

FIGURE 2. Comparison of functional status at time of angiography and currently in 19 surgically treated **(left)** and 9 nonsurgically treated survivors **(right).** Improvement in functional state occurred in each survivor in the surgical group, and more than half of the survivors are asymptomatic. Improvement in the condition of some nonsurgically treated patients was balanced by deterioration in others; however, none of the survivors are asymptomatic. The number of nonsurgically treated patients evaluated is smaller because of the greater mortality in that group.

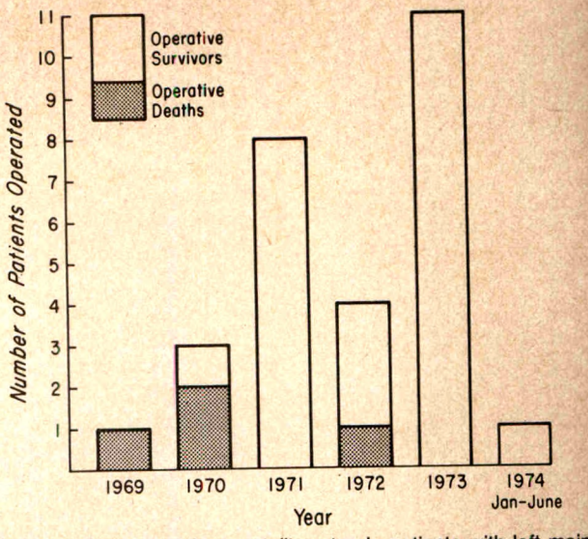

FIGURE 3. Early operative mortality rates in patients with left main coronary artery disease were high. However, since the beginning of 1971, only one patient, a man with unstable angina and diffuse coronary disease, has died at operation.

age. The difference in survival data is not statistically significant.

Discussion

Coronary Arteriography

The potential for sudden death during coronary arteriography in patients with left main coronary artery disease has been demonstrated.[1,2] However, a high mortality rate is not inevitable because similar patients studied with use of the Sones technique exclusively or a combination of the Sones and Judkins techniques have had a low mortality rate.[3,4] It has been suggested that the Judkins technique is inappropriate for use in patients with left main coronary artery disease.[2] Although complication rates may vary from one laboratory to another, this review of a 7 year experience using the Judkins technique exclusively with no deaths during 83 angiographic studies and a single death 3 days after angiography establishes that the technique can be performed at low risk in the presence of left main coronary artery disease. The relation of the single death to coronary angiography is uncertain. Our experience is similar to that of Webster et al.,[13] who reported that no deaths occurred during 29 studies at the Cleveland Clinic but that two patients died 1 and 3 days, respectively, after angiography.

Prediction of Left Main Coronary Artery Disease

The suggestion that special precautions be taken during angiography in patients with left main coronary artery disease presumes that the presence of the lesion can be accurately predicted or suspected. Severe or nocturnal angina, marked S-T segment depression during stress electrocardiography and left main coronary arterial calcification have been suggested as indicators of the lesion.[1,2] Although severe angina was found in 44 percent of our patients and its presence should alert the physician to the possibility of left main coronary artery disease, it is not a sensitive marker since 56 percent of our patients had less than severe angina and three patients had no angina. Conversely, in a group of 55 patients with unstable angina, only 2 had left main coronary artery disease.[14] Only two of our patients had marked S-T segment depression during stress electrocardiography. This finding may reflect our procedure of continuously monitoring the electrocardiogram during exercise and stopping the test as soon as diagnostic abnormalities appear rather than after completion of a predetermined work load.[10] Marked S-T segment depression may be caused by widespread disease in other major coronary arteries as well as by left main coronary artery disease.[15] Calcification of the left main coronary artery was found in 12 (21 percent) of our patients and is a reliable but insensitive marker of the disease. Because left main coronary artery disease may be found in patients with no angina and with normal resting and stress electrocardiograms, all patients undergoing coronary angiography must be approached as patients with left main coronary artery disease. The elements of a proper approach have been reviewed elsewhere.[16,17]

Angiographic Features Relating to Prognosis

The poor prognosis of patients with left main coronary artery disease must be attributed either to an intrinsic characteristic of the lesion such as its proximal location or a propensity to rapid progression of disease or to some factor commonly found in association with it that produces its lethal effect alone or in concert with the lesion.

Hydraulic analysis suggests that the reduction in blood flow caused by stenosis of a major trunk vessel is no greater than the reduction in flow caused by comparable stenoses in each branch vessel.[18] There-

fore, left main coronary artery disease should have an effect on flow to an extent similar to that caused by equal degrees of obstruction in the left anterior descending and circumflex coronary arteries. Analysis of the angiograms of our 25 patients who had two angiographic studies demonstrates that the rate of progression of disease in the left main coronary artery is no greater than that in other major coronary arteries and cannot by itself explain the poor prognosis in this lesion.

A striking feature of patients with left main coronary artery disease was the *extent of coexisting disease* in other major coronary arteries. In eight (13 percent) of our patients coexisting disease was so severe that it precluded surgery and these patients had a very poor prognosis. It has been demonstrated that the prognosis of patients with left main coronary artery disease is similar to that reported in patients with three vessel disease alone.[3] Although progression of disease in the left main coronary artery alone may not be rapid, small changes in the left main coronary artery and one of its branches occurring simultaneously may have a critical effect on flow because critical stenoses in series are additive in their effects on flow.[19] For all these reasons, we believe that the poor prognosis of patients with left main coronary artery disease is largely related to the high frequency of severe coexisting coronary artery disease. The prognosis of isolated left main coronary artery disease found in only two of our patients is unknown because of the small number of cases available for analysis.

Efficacy of Surgical Therapy

An appropriate assessment of the benefits of surgery can be made by comparison of patients treated with and without surgery only after exclusion of those patients who are not surgical candidates. The prognosis of this latter group is unlikely to be altered by surgical therapy and is extremely poor. Inclusion of patients with inoperable conditions in the nonsurgical group does not allow comparison of patients at equal risk. The surgically treated group had a reduced frequency of angina in contrast to the nonsurgically treated patients in whom angina persisted. The effect of surgery on survival, as shown in Figure 1, was not statistically significant but may be greater than indicated because our early experience with saphenous vein bypass grafting, in which there was a high operative mortality rate, is included (Fig. 3). Since the end of 1970, there have been 23 operative survivors among 24 patients with left main coronary artery disease, and the estimated survival rate of these patients 3 years postoperatively is 78 percent rather than the 70 percent shown for the entire group. The improvement in survival data of the patients operated on more recently is largely the result of a reduction in operative mortality but may also reflect a tendency to perform bypass grafting in a greater number of obstructive lesions.

Comparisons of larger groups of surgically[4] and nonsurgically[3] treated patients suggest that saphenous vein bypass grafting prolongs life, but the suitability for surgery of the nonsurgically treated patients is not established[3] and the reported follow-up time of surgical survivors is short.[4] Also, comparison of groups of patients from different institutions may be misleading. Although achievement of low operative mortality rates now appears possible, further follow-up will be required to determine whether the propensity to widespread disease in these patients may offset the effects of successful surgery.

Conclusions

We conclude: (1) All patients undergoing coronary angiography should be considered to have left main coronary arterial stenosis and appropriate precautions should be taken because clinical findings suggested as predictors of left main coronary artery disease were found in less than half of our patients. Uncommonly, left main coronary artery disease may be found even in the angina-free patient. (2) Coronary arteriography can be performed at low risk with either the Sones or Judkins technique in the presence of left main coronary artery disease if careful technique is observed. (3) A major factor in the poor prognosis of patients with left main coronary artery disease is the frequent presence of associated disease in other major coronary arteries. In our group of 58 patients, the condition of 13 percent was inoperable for this reason. Extrapolation from clinical precepts derived from the majority of patients with severe coexisting disease to the occasional patient with isolated left main coronary artery disease may not be warranted. (4) At present, an improved survival rate with surgery cannot be demonstrated. However, the operative risk is low and the majority of patients operated on are free of angina.

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Variant Angina Pectoris: Clinical and Anatomic Spectrum and Results of Coronary Bypass Surgery

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Twenty patients are described with the variant angina syndrome (recurrent angina at rest with S-T segment elevations occurring only during pain and no evolution of infarction). In contrast to patients previously reported on, all but one had progressive unstable angina before hospitalization. Angina was frequently associated with arrhythmias, including ventricular fibrillation (2 instances), ventricular tachycardia (4), frequent ventricular premature beats (5), atrioventricular block (4), sinus bradycardia (2), sinoatrial exit block (1) and supraventricular tachycardia (1). Seventeen patients had significant proximal stenosis of one or more coronary arteries with good distal vessels. Bypass surgery in 15 of these patients resulted in one noncardiac postoperative death, one perioperative infarction and relief of pain in all 14 survivors. After a 17 month mean follow-up period (range 4 to 38 months), all survivors are pain-free. Three patients had no significant coronary disease; one of these became asymptomatic with medical therapy, one continues to have angina and one died suddenly. Patients with normal coronary arteries could not be distinguished clinically or by electrocardiogram from those with severe obstructive lesions. This experience suggests that all patients with the variant angina syndrome should be studied by coronary angiography, and that most patients with significant fixed coronary lesions will do well after coronary bypass surgery.

In 1959, Prinzmetal et al.[1] described a form of variant angina pectoris characterized by pain occurring at rest or during ordinary activity rather than with exertion. The electrocardiogram during this variant angina showed S-T segment elevations with prompt return to control levels upon remission of pain. Since there was no evolution of myocardial infarction and since the course was believed to be stable or to improve with time, this type of angina was differentiated from "preinfarctional angina." However, many studies have indicated[2–9] that subsequent infarction in areas in which S-T-segment elevations were observed frequently occurs and that mortality in the follow-up period is significant.

Since Prinzmetal's original description, coronary angiography and coronary artery bypass surgery have come into general use. However, the roles of medical and surgical therapy in this syndrome are controversial, and it has recently been suggested that the latter is not appropriate for the majority of these patients.[10] This paper therefore describes the clinical spectrum, angiographic features and results of medical and surgical therapy in 20 patients admitted to the Massachusetts General Hospital with the variant angina syndrome, 15 of whom had coronary bypass surgery.

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TABLE I

Clinical Data on 20 Patients with Variant Angina Pectoris

Case no.	Age (yr) & Sex	Duration of Angina	Duration of Accelerated Angina	Exertional Angina	Pain Relief with NTG	S-T Elevations	Arrhythmias During Pain
			Anterior or Anterolateral S-T Elevations				
1	54M	1 month	1 hour	Yes	Yes	V_1—V_6	VF
2	54M	8 months	1 week	Yes	Yes	I, aVL, V_1—V_4	VT
3	58M	1 year	5 days	No	Yes	V_1—V_5	VPBs
4	64F	1 week	1 week	No	Yes	V_1—V_4, aVL	...
5	58F	1 hour	1 hour	No	No	I, aVL, V_1—V_4	SB, VPBs
6	50F	10 years	3 weeks	Yes	Yes	V monitor	VT
7	53M	3 weeks	2 days	Yes	Yes	V_1—V_6	SAB
8	58M	4 years	1 month	Yes	Yes	aVL, V_2—V_6	...
9	49M	2 days	2 days	Yes	Yes	I, aVL, V_5—V_6	...
10	52F	8 days	8 days	Yes	Yes	I, aVL, V_2—V_6	...
11	56F	1 hour	1 hour	Yes	Partial	V_2—V_6	...
12	59F	12 hours	12 hours	No	Partial	V_1—V_6	VPBs, SVT, AF
			Inferior or Inferoapical S-T Elevations				
13	55M	2 years	Few hours	Yes	Yes	II,III, aVF	2° AVB, VT, VF
14	45F	2 weeks	2 weeks	No	No	II,III, aVF	SB, SA
15	44M	3 years	1 week	Yes	Partial	II,III, aVF	VPBs
16	53F	4 months	...	Yes	Yes	II,III, aVF	SA, SB, 3° AVB
17	39F	18 months	1 month	Yes	Yes	II,III, aVF	VPBs
18*	42F	6 months	1 hour	No	Yes	II,III, aVF	2° AVB
19*	45F	2 weeks	1 hour	No	Yes	II,III, aVF	SB, 2° AVB, VT
20*	58F	4 years	3 weeks	No	Yes	II,III, aVF, V_5—V_6	...

*Patients without significant coronary artery disease.

AF = atrial flutter; AVB = atrioventricular block; NTG = nitroglycerin; SA = sinus arrest; SAB = sinoatrial block; SB = sinus bradycardia; 2° = second degree; SVT = supraventricular tachycardia; 3° = third degree; VF = ventricular fibrillation; VPBs = ventricular premature beats; VT = ventricular tachycardia.

Patient Selection

Twenty patients admitted to the Massachusetts General Hospital from January 1971 to January 1974 fulfilled the criteria for variant angina pectoris: recurrent angina at rest associated with S-T segment elevations, not in the area of an old infarction, with return of the S-T segments to control levels after relief of pain, and without evolution of myocardial infarction by serial electrocardiograms or by cardiac enzymes. These patients were 8 men averaging 53 years of age and 12 women averaging 52 years of age. All patients had selective coronary angiography. Seventeen patients had significant obstructive coronary lesions, that is, greater than 70 percent luminal narrowing. Three patients had no significant coronary artery disease by angiogram.

Results with Comment

History and Physical Examination

The clinical characteristics of these patients are shown in Table I. The total duration of angina ranged from 1 hour to 10 years. All patients had angina at rest, frequently at a predictable time of day. In contrast to the stable course depicted in Prinzmetal's original description,[1] all but one of the patients in this series (Patient 16, who had stable angina over a 4 month period) had progressive, unstable angina for 1 hour to 1 month, leading to hospitalization for increasing frequency and duration of severe pain. Although previous reports have described exertional pain only rarely in variant angina,[4,8,10,11–14] 12 of our patients had angina on exertion as well as during rest; in 7, the pain began with exertion only and progressed to pain during rest. All 12 of these patients had significant obstructive coronary lesions. The three patients with angiographically normal arteries (Patients 18 to 20) had pain only during rest. Pain was completely relieved by nitroglycerin in 15 patients; 2 had no response and 3 had only partial relief.

Physical examination of the cardiovascular system was normal except for the presence of an apical fourth heart sound gallop in 10 patients. All three patients with variant angina and no significant coronary artery disease were female.

Electrocardiographic Findings

Figure 1 shows the course of S-T segment changes during and after pain in Patient 19, who had angiographically normal coronary arteries. Similar S-T elevations during pain occurred inferiorly or inferoapically in 8 patients and anteriorly or anterolaterally in 12 patients (Table I). Concurrent S-T depressions appeared in reciprocal leads in all. The three patients

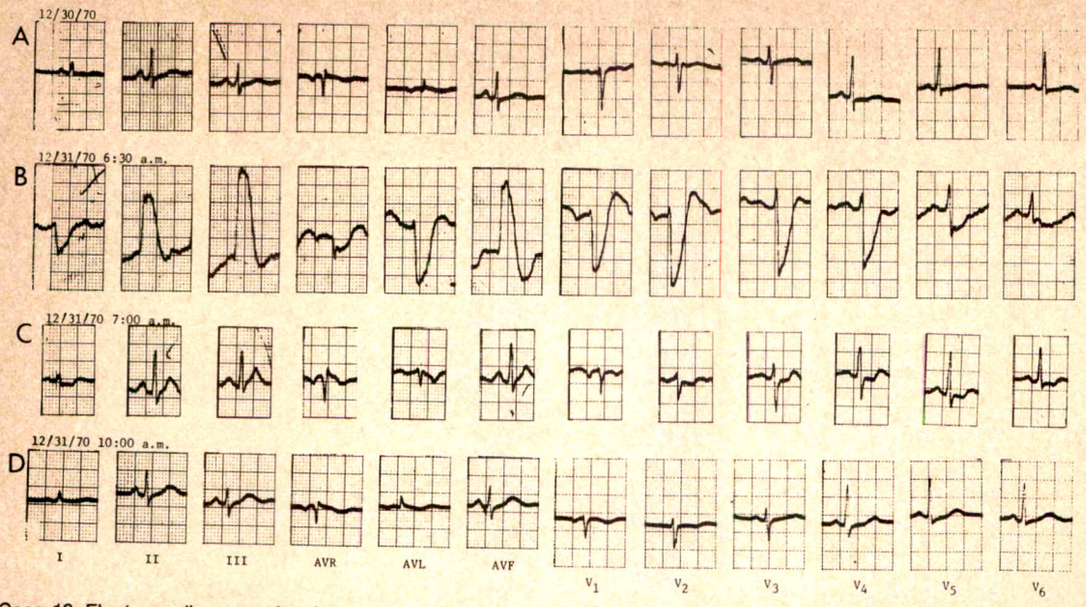

FIGURE 1. Case 19. Electrocardiograms showing representative changes in S-T segments during pain. **A,** in the absence of pain. **B,** during pain, showing marked S-T elevations in the inferior leads with reciprocal depressions anterolaterally. **C,** 30 minutes later, after relief of pain, showing persistent slight anterolateral S-T depressions. **D,** return to normal 3 hours later.

TABLE II

Cardiac Catheterization Data and Course of 20 Patients with Variant Angina Pectoris

Case no.	Location of Significant Coronary Lesions	Left Ventricle	Coronary Vessels Bypassed	Follow-Up Data
		Anterior or Anterolateral S-T Elevations		
1	Proximal LAD	Normal	LAD	No angina, 25 mo.
2	Proximal LAD, LAD diagonal, LCxM	. . .	LAD, LAD diagonal	No angina, 19 mo.
3	Proximal LAD	. . .	LAD	No angina, 22 mo.
4	Proximal LAD	. . .	LAD	No angina, 14 mo.
5	Proximal LAD	Inferoapical aneurysm	LAD	No angina, 22 mo.
6	Proximal LAD, RCA	Normal	LAD	No angina, 38 mo.
7	Proximal LAD; occluded RCA	Inferoapical akinesis; slight anterolateral hypokinesis	LAD, RCA	No angina, 9 mo.
8	Proximal LAD, LCx	Normal	None	No angina, 7 mo.
9	Proximal LAD, LAD diagonal; occluded RCA	Slightly enlarged; inferior akinesis; anterolateral hypokinesis	LAD, RCA	No angina, 6 mo.
10	Proximal LAD; occluded RCA	Anterolateral hypokinesis; apical dyskinesis	LAD	No angina, 4 mo.
11	Proximal LAD, LCxM; occluded RCA	Slight enlargement; inferior akinesis; anterolateral and apical hypokinesis	LAD, LCxM, RCA	Died postop
12	Proximal LAD, LCxM	Apical akinesis; inferior hypokinesis	LAD, LCxM	No angina, 11 mo.
		Inferior or Inferoapical S-T Elevations		
13	LCA ostium, distal RCA	Inferoapical hypokinesis	LAD, RCA	No angina, 20 mo.
14	Proximal LAD, LCx and RCA	Normal	LAD, LCx, RCA	MI with anesthesia preop
15	Proximal LAD, mid RCA	Inferoapical akinesis	LAD, RCA	No angina, 10 mo.
16	Proximal LAD, LAD diagonal, mid RCA	Inferior hypokinesis	LAD, RCA	No angina, 5 mo.
17	Proximal LCx, LCxM	Normal	None	No angina, 5 mo.
18	None	Normal	None	Recurrent angina, 17 mo.
19	None	Normal	None	No angina, 40 mo.
20	None	Normal	None	Died suddenly, 8 mo.

LAD = left anterior descending coronary artery; LCA = left coronary artery; LCx = left circumflex artery; LCxM = left circumflex marginal artery; MI = myocardial infarction; postop = postoperatively; preop = preoperatively; RCA = right coronary artery.

without significant coronary disease angiographically (Patients 18 to 20) had S-T elevations inferiorly, a finding reported in the majority of patients with variant angina and insignificant coronary disease.[2–4,10–13,15–18] Nevertheless, four such patients had anterior S-T elevations.[2,11,18,19] Thus, the location of S-T elevation does not predict presence or absence of fixed obstructive coronary lesions. In the other 17 cases, the location of S-T elevation correctly predicted a cardiac area supplied by a significantly obstructed coronary artery. However, several patients (Cases 6, 7, 9 to 11, 13 to 16) had additional significant coronary disease that was not predicted by the leads showing S-T elevations (Table II).

The electrocardiogram in the absence of pain returned to normal in 6 patients, including the 3 without significant coronary disease, and showed persistent nonspecific S-T segment and T wave abnormalities in the other 14. In no cases did new Q waves develop, nor was there serial evolution of nontransmural infarction. Four patients (Cases 2, 7, 9 and 11) had electrocardiographic evidence of an old inferior wall infarction; all four had S-T elevations in the anterior leads during variant angina.

Serious arrhythmias during episodes of pain were common (Table I). With pain, ventricular fibrillation occurred in two patients and ventricular tachycardia in four, including one patient without significant coronary disease angiographically (Case 19). Five additional patients had frequent ventricular premature beats during pain. Whether ischemia involved the anterior or inferior wall did not appear to affect the incidence of ventricular irritability. Second degree atrioventricular (A-V) block of the Wenckebach type occurred in three patients, including two with angiographically normal coronary arteries. Intermittent complete A-V block occurred in one patient. All four patients with A-V block had evidence of inferior wall ischemia. Marked sinus bradycardia during pain occurred in two patients with inferior and in one patient with anterior ischemia. Sinoatrial (S-A) exit block of the Wenckebach type was seen in one patient with anterior ischemia. One patient had periods of supraventricular tachycardia during pain.

The frequency of arrhythmias in our patients is in accord with data from previous studies in which ventricular irritability,[3,4,7,8,10,15,16,19] atrial fibrillation,[4,9,14] supraventricular tachycardia,[10,11] second and third degree A-V block,[3,4,10–12,16,17,20–22] extreme sinus slowing[18] and S-A block[22] have been reported.

Angiography

Coronary angiographic data are summarized in Table II. Seventeen patients had greater than 70 percent fixed obstruction of a major coronary artery. Five patients had significant disease of one major coronary vessel only (Cases 1, 3 to 5 and 17). Nine patients had significant disease of two major arteries with the left anterior descending artery being involved in all (Cases 2, 6 to 10, 12, 15 and 16). Three patients (Cases 11, 13 and 14) had the equivalent of significant three vessel disease. All patients had adequate distal vessels and none had diffuse inoperable disease. Three patients (Cases 18 to 20) had no angiographically significant coronary disease. The occurrence of multiple vessel obstructive disease is in contrast to Prinzmetal's suggestion that variant angina is associated with severe disease of a single coronary artery only.[1] Indeed, the distribution of coronary lesions in these patients does not appear to differ from that in patients with typical exertional angina, except for the absence of diffuse distal disease.

Left ventricular angiograms were performed for all but three patients and were normal in eight. Four patients with old inferior infarction had evidence of inferior wall akinesis or dyskinesis. Eight patients had evidence of hypokinesis in the left ventricular areas supplied by stenotic vessels (Table II).

Coronary spasm is often postulated to be an etiologic factor in initiation of pain in patients with variant angina. This was not observed in any of our patients; however, none of our patients experienced angina during angiography. Prinzmetal et al.[1] originally proposed that pain was due to "temporarily increased tonus of a single large narrowed coronary artery." More recently, spasm has been demonstrated to occur during coronary angiography of patients with variant angina, either in an essentially normal vessel[16,22] or in the area of a plaque that did not cause significant obstruction in the absence of spasm.[10] Thus, spasm may be an important factor, at least in patients with the syndrome of variant angina and normal coronary arteries. The role of spasm in patients with significant fixed obstructive lesions is not known. Experimental studies of coronary occlusion in dogs have indicated that S-T elevations are indicative of more severe myocardial ischemia than are S-T depressions.[23] Possibly, the combination of spasm and fixed obstruction might result in greater ischemia.

Hospital Course

Medical treatment: After admission to the hospital, despite absolute bed rest, angina associated with S-T elevations continued to occur in all patients but one (Case 6). Four patients (Cases 8, 13, 14 and 19) had no further pain on treatment with long-acting nitrates and propranolol in doses of 80 to 160 mg/day. One patient (Case 17) continued to have angina with propranolol in a dose of 320 mg/day but not when the dose was increased to 560 mg/day. Two patients (Cases 7 and 20) had a marked decrease in frequency and severity of pain with long-acting nitrates alone. The other patients continued to experience angina with propranolol (40 to 320 mg/day) and, in most cases, long-acting nitrates. Because of continued pain at rest in spite of intensive medical therapy, 10 patients underwent intraaortic balloon pumping before angiography. This procedure resulted in cessation of pain in all but two patients, one with continued significant pain (Case 4) and one with persistent mild pain (Case 2).

Bypass surgery: Because of the unstable progressive severity of their angina and the frequently asso-

ciated arrhythmias despite intensive medical therapy in most cases, 15 of the 17 patients with significant coronary lesions underwent coronary arterial bypass grafting. Two patients (Cases 8 and 17) received only medical therapy in spite of anatomic features suitable for bypass grafting. Six patients had single vein grafts, all to the left anterior descending coronary artery. Seven patients had double grafts, to the left anterior descending and right coronary arteries in five, to the left anterior descending artery and its diagonal branch in one and to the left anterior descending and circumflex arteries in one. Two patients had triple grafts to the left anterior descending, left circumflex and right coronary arteries. There was one in-hospital death (due to severe pulmonary infection and renal failure). One patient (Case 14) had an intraoperative myocardial infarction related to failure of a temporary pacemaker to function when complete A-V block occurred during induction of anesthesia. All others tolerated the bypass procedure well.

Follow-Up

All 14 patients surviving bypass surgery are living after an average follow-up period of 17 months (range 4 to 38 months) and all are pain-free (Table II). No patient has had further difficulties with arrhythmias, and no myocardial infarctions have occurred postoperatively. The favorable postoperative course of these patients differs from previously reported experiences. Five of the six patients with bypass surgery described by McAlpin et al.[10] had pain at rest within 4 weeks, associated with occlusion of the graft in three and occlusion of the vessel just distal to the graft in another. Recently, Bodenheimer et al.[12] reported that two of three patients with bypass grafting had continued pain postoperatively, one with a perioperative infarction and one with an occluded graft. Betriu et al.[11] described a patient with bypass grafting who had a postoperative infarction and continued angina with an occluded graft.

The two patients in our series with significant obstructive lesions treated medically are asymptomatic, one (Case 8) 7 months after admission on a regimen of isosorbide dinitrate and propranolol, 160 mg/day, and one (Case 17) 5 months after admission on a regimen of isosorbide dinitrate, quinidine and propranolol, 560 mg/day. Prinzmetal et al.[1] and, more recently, McAlpin et al.[10] suggested that the clinical course in these patients is rather stable and that their symptoms tend to decrease with time. The latter investigators therefore recommended that surgery be reserved only for patients with incapacitating symptoms refractory to medical therapy. In contrast, review of other reported cases indicates a high incidence of infarction and death for patients given medical therapy alone.[2–9] We hope that successful bypass surgery will alter this unfavorable prognosis.

Patients without significant coronary artery disease: Of the three patients in this group, one (Case 19), who had multiple episodes of ventricular tachycardia during pain, has had gradual disappearance of symptoms and is doing well 40 months after admission on therapy with isosorbide dinitrate, propranolol, quinidine and diphenylhydantoin. Another (Case 18), after several months without pain, again experienced frequent anginal episodes relieved by nitroglycerin; long-acting nitrates could not be employed because of severe headaches associated with their use. The third patient (Case 20) died suddenly during an episode of pain 8 months after hospitalization while receiving long-acting nitrates.

Patients having angina pectoris in association with evidence of myocardial ischemia but with normal coronary angiograms have been reported to follow a benign course.[24,25] Whether the occurrence of S-T elevations during pain is associated with a more unfavorable course in such patients with normal coronary arteries is unknown. The association of A-V block or serious ventricular arrhythmias, or both, with pain in two of our three patients without significant coronary disease, and in most of the similar isolated cases previously reported,[3,4,15–17,19] appears to indicate a severe degree of ischemia in these patients, perhaps related to occlusive spasm. Although the condition of two of our patients improved with time after medical therapy, as has that of some other similar patients,[11,12,17,18] one of our patients and four described by others[4,15,18,19] died suddenly during anginal episodes. Surgery does not appear to be indicated for these patients. Dhurandhar et al.[15] described such a patient with documented proximal right coronary arterial spasm only who had bypass grafting to the distal right coronary artery. Ten days postoperatively recurrent variant angina developed, and he died with the graft remaining patent. Recently, Betriu et al.[11] reported on three patients with nonsignificant obstructive lesions who underwent bypass grafting; one died postoperatively, one had recurrence of pain and one had a postoperative infarction with an unknown subsequent course. The demonstration by Oliva et al.,[17] in a patient having the variant angina syndrome with normal coronary arteries in the absence of pain, that the site of spasm during pain varied and at times involved a long segment of the right coronary artery extending as far distally as the posterior descending artery, may explain the ineffectiveness of bypass grafting in these patients.

Conclusions

Our experience suggests that all patients with the variant angina syndrome should be studied by coronary angiography since no clinical or electrocardiographic manifestations could distinguish those patients with angiographically normal coronary arteries from those with severe proximal obstructive lesions. In contrast to findings in most previous reports, all but one of our patients had an unstable and progressive course. Although our patients were inevitably a selected group, since their angina was severe enough to result in hospitalization, the same is true of other series. Patients with severe proximal obstructive lesions can undergo coronary artery bypass surgery with a low risk and excellent postoperative course over a prolonged follow-up period.

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Oxygen Delivery, Anoxic Metabolism and Hemoglobin-Oxygen Affinity (P_{50}) in Patients with Acute Myocardial Infarction and Shock

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Changes in systemic oxygen delivery after acute myocardial infarction were investigated in 21 patients. In seven patients with shock, circulatory failure was characterized by a significant reduction in cardiac index, a decrease in oxygen transport and oxygen consumption and an increase in concentration of blood lactate; a decrease in the affinity of hemoglobin for oxygen (increased P_{50}) was also noted. The P_{50} averaged 28.8 ± 0.87 (standard error of the mean) torr in patients with shock and 26.0 ± 0.45 torr ($P < 0.05$) in patients without circulatory failure. However, there was no significant difference in oxygen extraction from arterial blood between the two groups.

The time course of the changes in P_{50}, cardiac index and oxygen consumption was separately examined in 12 patients. In six patients with shock, P_{50} increased by an average of 4.6 ± 2.05 torr ($P < 0.05$) and this augmentation accounted for an estimated 18 percent increase in oxygen release. Maximal P_{50} values were observed after 24 hours of circulatory failure. In the absence of shock, no consistent changes in P_{50}, cardiac index or oxygen consumption were observed.

These data indicate that a reduction in oxygen delivery after acute myocardial infarction is followed by a compensatory increase in P_{50}. This change in P_{50} accounts for increases in oxygen availability independently of changes in cardiac output.

Circulatory failure after acute myocardial infarction is associated with a critical reduction in the viable mass of left ventricular myocardium.[1] Previous studies have documented that a decrease in cardiac output usually follows an acute infarction.[2,3] The extent to which this reduction in cardiac output is a critical determinant of survival is contingent on a concurrent reduction in oxygen availability.[4–6] Hence, pulmonary gas exchange, circulating hemoglobin and the affinity of the hemoglobin for oxygen constitute important variables in addition to cardiac output.[7]

The affinity of hemoglobin for oxygen is quantitatively assessed by P_{50}, the oxygen tension at which the hemoglobin is 50 percent saturated with oxygen. P_{50} is a major determinant of the position of the oxyhemoglobin equilibrium curve, which in turn influences the arteriovenous oxygen difference [$C(a\text{-}\bar{v}\ DO_2)$]. Increases in P_{50} indicate a rightward shift of the oxyhemoglobin equilibrium curve and therefore a decrease in the affinity of hemoglobin for oxygen. This favors oxygen unloading, thus increasing $C(a\text{-}\bar{v}\ DO_2)$ and oxygen delivery to tissues. Similarly, decreases in P_{50} indicate a leftward shift of the oxyhemoglobin equilibrium curve and therefore increased affinity of hemoglobin for oxygen.[7–9]

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TABLE I

Clinical Data

Case no.	Age (Yr) & Sex	Location of AMI	Past History	AMI-HS Interval (hr)	MAP* (torr)	UO† (ml/hr)	Clinical Course
1	79F	Ant	CHF	26	62	14	Survived
2	75M	Ant	···	18	62	20	Died
3	73F	Ant	H, CHF	233	83	12	Died
4	76F	Inf	···	96	57	·21	Died
5	80F	Inf	H, D	12	78	20	Died
6	57F	Ant	D	19	54	17	Died
7	74F	Inf	H	6	86	12	Died
8	51M	Inf	H	7	103	40	Survived
9	57F	Inf	AMI	20	63	46	Survived
10	47M	Ant	AMI	48	97	46	Survived
11	85M	Ant	···	144	68	38	"Pump" failure, died on 9th day
12	64M	Ant	···	19	85	100	CHF; survived
13	75M	Inf	AMI, D	24	85	206	Died of noncardiac cause
14	53F	Inf	···	18	85	46	Survived
15	49M	Ant	···	77	87	50	CHF, pericarditis; survived
16	72F	Inf	···	6	110	100	Sudden death on 6th day
17	70M	Ant	···	12	80	50	Ruptured left ventricle; died
18	64M	Inf	AMI	13	75	38	Survived
19	74M	Ant	···	6	85	242	Pulmonary edema; survived
20	53M	Inf	···	21	62	38	Survived
21	65M	Ant	CHF	15	64	100	Extension of AMI; died on 10th day

*Values obtained at initial hemodynamic study.
†Values obtained within 4 to 6 hours of initial study.
AMI = acute myocardial infarction; Ant = anterior; CHF = prior congestive heart failure; D = diabetes mellitus; H = arterial hypertension; HS = hemodynamic study; Inf = inferior; MAP = mean arterial pressure; UO = urinary output.

Recently, increases in P_{50} have been observed in patients with heart failure and acute myocardial infarction[8,9] and have been interpreted as a compensatory mechanism for increasing oxygen availability when systemic blood flow is reduced. This study was undertaken to quantitate the extent to which these changes in P_{50} compensate for decreases in cardiac output and modify the course of circulatory failure.

Material and Methods

Patients

Twenty-one patients admitted to the coronory care unit of the University of Southern California Center for the Critically Ill between November 1971 and December 1972 were the subjects of this study. There were 12 men and 9 women whose ages ranged from 47 to 85 (median 70) years. All 21 subjects had a diagnosis of acute myocardial infarction based on a typical clinical history, characteristic Q waves and S-T segment changes in the electrocardiogram and significant increases in serum creatine phosphokinase, glutamic oxaloacetic transaminase and lactic dehydrogenase. The clinical features of the 21 patients are summarized in Table I.

Seven patients had acute circulatory failure (shock), characterized by clammy skin, mental obtundation, reduction in intraarterial systolic pressure to less than 90 torr* or a decrease of more than 50 torr in patients who had systemic hypertension, urinary output of less than 30 ml/hour, and lactate concentration of arterial blood in excess of 1.4 millimole/liter. Four of the seven had anterior wall myocardial infarction and three had inferior wall infarction. Clinical signs of shock appeared after an estimated interval of 56 (2 to 216) hours after the onset of chest pain. Only one patient with shock survived.

Among the remaining 14 patients, 9 survived for 15 days or longer and 5 died, respectively, of ventricular arrhythmia, extension of the acute infarction, cerebral death after resuscitation from cardiac arrest, rupture of the left ventricle and progressive congestive heart failure.

* torr = pressure of 1 mm Hg at 0° C and standard gravity.

Methods

Initial hemodynamic studies were performed in 15 patients during the first 24 hours after the estimated time of infarction. In four patients the hemodynamic studies were undertaken after 48 hours (Table I). Informed consent was obtained from all patients. After local anesthesia with 2 percent lidocaine, a Swan-Ganz® catheter[10] was inserted into a basilic vein and advanced to the pulmonary artery; correct position was documented by characteristic pressure curves and chest roentgenograms. The femoral artery was cannulated percutaneously utilizing a thin-walled Teflon® catheter (B-D Longdwel, 18 gauge, internal diameter 1.05 mm, length 20 cm). Pressures were measured with a Statham P23Db transducer, in conjunction with a two channel (model 7702B) or eight channel (model 7878A) Hewlett-Packard medical recorder.

Cardiac output was determined by the dye-dilution technique using indocyanine green. The area under each dye curve was calculated by numerical integration.[11]

Blood was sampled simultaneously from the pulmonary and femoral arteries within 3 minutes after inscription of

TABLE II

Initial Hemodynamic and Metabolic Data

Case no.	CI (liters/min per m²)	Hb (g/100 ml)	Ca_{O_2} (vol %)	O_2TI (ml/min per m²)	$C(a\text{-}\bar{v}DO_2)$ (vol %)	ER (%)	VO_2(ml/min per m²)	LAC (mmole/liter)
				Acute Myocardial Infarction and Shock				
1	1.6	13.0	18.88	302	4.27	22	68	2.04
2	1.5	13.9	18.01	270	5.30	29	79	2.23
3	1.3	13.0	16.08	209	7.68	47	100	2.42
4	1.1	8.6	12.37	135	6.18	49	66	4.10
5	1.5	12.5	16.75	251	9.54	56	143	10.60
6	1.7	13.7	19.17	326	6.68	34	113	1.60
7	1.0	15.0	20.42	204	8.01	39	80	1.75
Mean	1.4	12.8	17.38	242.4	6.80	39.4	92.7	3.53
±SEM	±0.09	±0.76	±1.00	±24.6	±0.66	±4.54	±10.54	±1.21
				Acute Myocardial Infarction Without Shock				
8	1.9	15.0	20.67	393	5.95	28	113	1.72
9	1.9	12.8	14.93	284	7.21	48	137	1.40
10	3.6	17.3	23.06	830	6.11	26	219	0.92
11	1.7	13.6	18.23	310	7.94	43	135	0.69
12	2.1	15.8	20.19	424	6.47	32	136	1.10
13	3.8	14.0	19.31	734	4.96	25	188	1.88
14	2.8	12.4	15.88	445	5.60	35	157	0.49
15	2.6	15.4	20.62	529	6.37	30	164	1.15
16	1.6	15.6	21.29	341	9.70	45	155	1.71
17	2.4	14.0	18.26	456	6.30	34	157	1.00
18	1.6	14.6	17.60	282	8.39	47	134	1.88
19	1.4	16.2	22.52	315	6.17	27	86	1.06
20	1.7	15.0	20.21	344	6.98	34	119	0.76
21	2.6	13.6	17.01	442	5.37	31	140	1.00
Mean	2.3	14.6	19.27	437.7	6.68	34.6	145.7	1.19
±SEM	±0.20	±0.36	±0.64	±43.8	±0.34	±2.12	±8.65	±0.12
				Acute Myocardial Infarction and Shock vs. Acute Myocardial Infarction Without Shock				
P value	<0.01	<0.025	NS	<0.005	NS	NS	<0.005	<0.01

$C(a\text{-}\bar{v}DO_2)$ = arteriovenous oxygen difference; CI = cardiac index; CaO_2 = arterial oxygen concentration; ER = O_2 extraction ratio; Hb = hemoglobin concentration; LAC = arterial lactate; NS = not significant; O_2TI = O_2 transport index; *P* = probability; VO_2 = systemic O_2 consumption; SEM = standard error of the mean.

the dye curve. Blood gas analyses were completed within 15 minutes after blood withdrawal. The partial pressures of oxygen (PO_2) and carbon dioxide (PCO_2) and pH were measured at 37° C with the standard electrode technique utilizing a Radiometer system (Radiometer Company, Denmark, model PHA 927). The saturation of hemoglobin with oxygen (SO_2), carboxyhemoglobin saturation and hemoglobin concentration (Hb) were measured with a spectrophotometer (Co-Oximeter, model 182, Instrumentation Laboratories).

Oxygen concentration was calculated by the formula: $Hb \times \%SO_2 \times 1.39 + PO_2 \times 0.0031$. The oxygen transport index was computed as the product of the arterial oxygen concentration and cardiac index.[12] The oxygen consumption index was calculated by cardiac index $\times C(a\text{-}\bar{v}\ DO_2) \times 10$. The percent of oxygen extracted from the arterial blood was calculated from the ratio of $C(a\text{-}\bar{v}\ DO_2)$ and arterial oxygen concentration and expressed as extraction ratio. Lactate was measured by a semiautomated adaptation of the technique of Marbach and Weil.[13]

P_{50}(pH 7.40 and 37° C) was calculated by the formula[14] $P_{50} = 26.6 \times PO_2C/PO_2S$, in which PO_2C represents the measured PO_2 of a venous sample corrected to standard conditions and PO_2S is the PO_2 corresponding to the measured oxygen saturation (corrected for carboxyhemoglobin) on the standard oxyhemoglobin equilibrium curve as obtained with the aid of a computer program.[15] The resultant value for P_{50} was defined as the "calculated" P_{50}. The method by which P_{50} is computed from single measurements of pH, PO_2 and SO_2 of venous blood has recently been validated in this laboratory.[16] The standard deviation of the differences between the "calculated" P_{50} and the "actual" P_{50} for 92 samples of blood with saturations between 20 and 90 percent was ±1.0 torr. In this study the "actual" P_{50} was obtained in three different ways: (1) The PO_2 was plotted against SO_2 and the P_{50} was read from the curve of best visual fit using the points of SO_2 between 20 and 90 percent; (2) by Hill's equation[17]; and (3) as the mean of four to six calculated P_{50} values. There was no significant difference between the P_{50} values obtained in these three ways.

The Student *t* test for unpaired data was used for statistical comparisons between groups of patients and the paired Student *t* test for comparisons of sequential measurements in the same group of patients.

Results

Cardiac output, oxygen availability and anoxic metabolism: The cardiac and oxygen transport indexes were significantly decreased in patients with

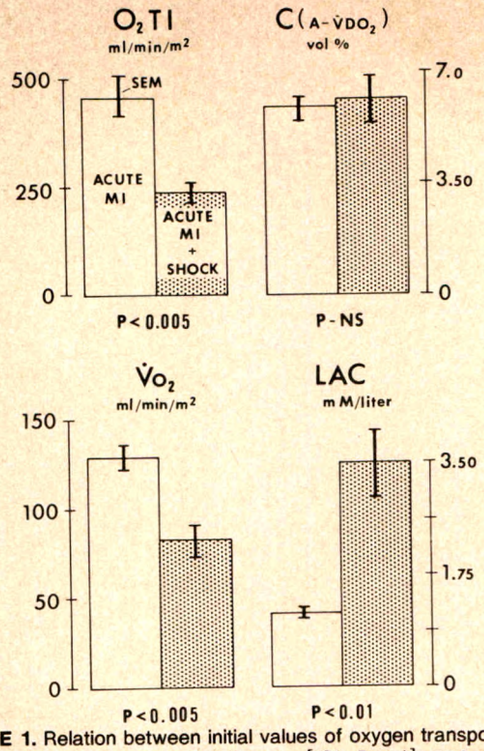

FIGURE 1. Relation between initial values of oxygen transport index (O_2TI), arteriovenous oxygen difference [$(C(A-\bar{v}DO_2)]$, systemic oxygen consumption ($\dot{V}_{O_2}$) and arterial lactate concentration (LAC) in 7 patients with myocardial infarction and 14 patients with infarction complicated by shock. NS = not significant; P = probability; SEM = standard error of the mean.

shock by comparison with values in patients without shock (Table II). However, arterial oxygen concentrations were not significantly different in the two groups of patients. The lower hemoglobin concentrations in patients with shock were in part related to the multiple blood samples removed for laboratory studies. Reductions in the oxygen transport among patients with circulatory failure were therefore related to reductions in cardiac output and, to a lesser extent, to lowering of hemoglobin concentration. Oxygen consumption was significantly reduced in patients with circulatory failure and this was associated with a concurrent increase in blood lactate. The reduction in cardiac output was only partially compensated for by increases in $C(a-\bar{v}\ DO_2)$ and the oxygen extraction ratio (Table II, Fig. 1).

In the absence of shock, the cardiac index was only slightly reduced and the oxygen consumption was within normal limits, confirming previous observations by Valentine et al.[18] Arterial blood lactate was normal in 10 patients, indicating that the oxygen uptake was sufficient for maintenance of aerobic metabolism. The lactate values were slightly increased to levels from 1.4 to 1.9 millimoles/liter in four patients, two of whom were among the five who died.

P_{50} and oxygen extraction: When patients with shock were compared with those without shock, a difference in P_{50} was noted (Table III). P_{50} was significantly higher ($P < 0.05$) and the affinity of hemoglobin for oxygen thereby less among those with shock.

TABLE III

Initial Values of Respiratory and Metabolic Variables

Case no.	Rectal Temp. (°C)	pH_a (units)	$P\bar{v}_{O_2}$ (torr)	$S\bar{v}_{O_2}$ (%)	P_{50} (torr)
Acute Myocardial Infarction and Shock					
1	38.0	7.46	48	80.0	26.4
2	39.0	7.28	49	65.0	29.7
3	39.0	7.47	28	46.0	24.0
4	37.5	7.49	30	51.0	27.7
5	37.1	7.29	28	41.0	27.8
6	36.5	7.47	37	65.0	30.7
7	37.3	7.47	34	59.0	29.7
Mean	37.7	7.41	36.3	58.1	28.0
±SEM	±0.35	±0.03	±3.38	±5.03	±0.87
Acute Myocardial Infarction Without Shock					
8	37.3	7.51	39	70.0	26.6
9	37.0	7.41	23	43.0	23.4
10	38.5	7.45	39	70.0	25.8
11	37.6	7.46	27	54.0	24.7
12	37.6	7.40	34	62.0	26.0
13	38.2	7.43	47	73.0	29.9
14	37.0	7.45	34	59.0	24.8
15	38.1	7.45	37	66.0	27.4
16	37.0	7.36	31	53.0	27.2
17	36.7	7.47	29	61.0	24.9
18	37.2	7.38	27	45.0	28.5
19	36.1	7.34	43	72.0	26.5
20	37.2	7.38	32	63.0	24.8
21	37.4	7.33	36	61.0	26.4
Mean	37.3	7.41	34.1	60.8	26.2
±SEM	±0.16	±0.01	±1.76	±2.51	±0.45
Acute Myocardial Infarction With Shock vs. Acute Myocardial Infarction Without Shock					
P value	NS	NS	NS	NS	<0.05

pH_a = arterial pH; $P\bar{v}_{O_2}$ = PO_2 in mixed venous blood; SEM = standard error of the mean; $S\bar{v}_{O_2}$ = oxygen saturation in mixed venous blood; Temp. = temperature.

The in vivo P_{50}, representing P_{50} at the patients' temperature and pH, was not significantly different from the P_{50} at 37° C and pH 7.40. Despite this increase in P_{50}, $C(a-\bar{v}\ DO_2)$ was not significantly higher among the patients in shock, thus suggesting that factors other than the affinity of hemoglobin for oxygen altered oxygen extraction.

Quantification of the effect of P_{50}: The specific effect of a rightward shift of the oxyhemoglobin equilibrium curve on oxygen availability was next examined. We compared the $C(a-\bar{v}\ DO_2)$ calculated on the basis of the oxygen saturation derived from the measured PO_2 according to the Severinghaus equation,[19] which assumes a normal P_{50}, with the $C(a-\bar{v}\ DO_2)$ obtained from the measured oxygen saturation. In 21 normal persons previously studied in our laboratory, the P_{50} averaged 27.0 ± 1.3 (standard deviation) torr. In 9 of the 21 patients in the present series, the P_{50} exceeded 27.0 torr, averaging 28.7 ± 0.42 (standard error of the mean) torr (Table II). The pH averaged 7.40 ± 0.02 units and the temperature 37.5 ± 0.25° C.

TABLE IV

Sequential Hemodynamic and Metabolic Data

Case no.	P_{50} (torr) a	P_{50} (torr) b	CI (liters/min per m²) a	CI (liters/min per m²) b	Hb (g/100 ml) a	Hb (g/100 ml) b	C(a-$\bar{v}$ DO_2) (vol %) a	C(a-$\bar{v}$ DO_2) (vol %) b	VO_2 (ml/min per m²) a	VO_2 (ml/min per m²) b	LAC (millimoles/liter) a	LAC (millimoles/liter) b	Interval a-b (hr)
Acute Myocardial Infarction and Shock													
1	26.4	37.0	1.6	1.6	13.0	10.0	4.27	6.35	68	102	2.04	1.65	22
2	29.7	37.5	1.5	1.1	13.9	11.8	5.30	9.77	79	107	2.23	5.30	48
3	24.0	32.6	1.3	1.2	13.0	10.0	7.68	8.60	100	103	2.42	2.50	69
4	27.7	27.6	1.1	1.5	8.6	11.6	6.18	6.37	66	96	4.10	1.30	7
6	30.7	33.0	1.7	2.1	13.7	11.0	6.68	5.33	113	112	1.60	2.31	44
7	29.7	28.3	1.0	1.0	15.0	15.0	8.01	7.48	80	75	1.75	6.73	4
Mean	28.0	32.6*	1.4	1.4	12.8	11.6	6.35	7.31	84	99*	2.35	3.29	32
±SEM	±1.02	±1.7	±0.10	±0.16	±0.90	±0.75	±0.57	±0.67	±7.56	±5.30	0.36	±0.89	
Acute Myocardial Infarction Without Shock													
8	26.6	26.6	1.9	2.3	15.0	14.3	5.95	5.27	113	121	1.72	2.80	24
9	23.4	30.0	1.9	1.4	12.8	10.0	7.21	6.45	137	90	1.40	0.82	34
11	24.7	33.8	1.7	1.5	13.6	13.8	7.94	6.77	135	101	0.69	0.82	5
12	26.0	26.5	2.1	2.4	15.8	16.2	6.47	8.20	136	197	1.10	0.95	23
15	27.4	28.0	2.6	2.9	15.4	14.6	6.37	5.37	164	157	1.15	1.43	5
21	26.4	26.3	2.6	3.0	13.6	13.0	5.37	5.0	140	150	1.0	1.0	16
Mean	25.7	28.5	2.1	2.2	14.4	13.6	6.55	6.17	137	136	1.17	1.30	18
±SEM	±0.59	±1.19	±0.15	±0.27	±0.48	±0.84	±0.37	±0.49	±6.62	±16.2	±0.14	±0.31	

* = $P < 0.05$ (a vs. b)

a = initial values; b = values obtained at the time of the highest P_{50}; CI = cardiac index; C(a-$\bar{v}$ DO_2) = arteriovenous oxygen difference; Hb = hemoglobin concentration; LAC = arterial lactate concentration; SEM = standard error of the mean; $\dot{V}O_2$ = oxygen consumption.

In these nine patients, the C(a-$\bar{v}$ DO_2) based on measured saturations exceeded calculated values by 1.07 ± 0.29 volumes percent ($P < 0.01$). Consequently, estimates of oxygen consumption based on measured oxygen saturations and simultaneous determinations of cardiac index were 20.0 ± 8.64 ml/min per m² ($P < 0.05$) greater than those based on calculated values of oxygen saturations. This is equivalent to a 19 percent increase in cardiac index.

P_{50} changes over time and their influence on oxygen availability: In 12 patients, including 6 who were in shock, adequate hemodynamic and metabolic measurements were available after the initial studies (Table IV). These data were used to further assess the extent to which increases in P_{50} might compensate for reductions in cardiac output. Results herein reported refer to maximal increases in P_{50} that were observed at intervals ranging from 4 to 69 hours after the initial measurements. Among the patients with shock, the average P_{50} increased by 4.6 torr ($P < 0.05$), the C(a-$\bar{v}$ DO_2) by 0.96 volume percent, and the oxygen consumption by 15 ml/min per m² ($P < 0.05$); the hemoglobin concentration was reduced in four of the six patients, but the differences were not statistically significant. Since there was no significant change in cardiac index, the increase in oxygen consumption was accounted for by the increased C(a-$\bar{v}$ DO_2). Although the oxygen consumption increased significantly, it still remained in a subnormal range and lactic acidosis persisted during the period of observation as an indication of persistent anaerobic metabolism. In the patients without shock no significant changes in P_{50}, cardiac index, C(a-$\bar{v}$ DO_2), oxygen consumption or lactate were observed.

When increases in P_{50} were observed in the absence of shock, cardiac output was usually decreased. In Patients 9 and 11, substantial increases in P_{50} followed concurrent reductions in cardiac output (Table IV). Once again, increases in P_{50} were related to reductions in systemic blood flow.

Discussion

In this study we confirmed a significant reduction in cardiac index among the patients with circulatory failure and further demonstrated a parallel reduction in oxygen transport and oxygen consumption. Oxygen consumption was calculated from cardiac output and arteriovenous oxygen difference rather than measured directly. In these critically ill patients, measurements that require the patient's cooperation, such as the direct measurement of oxygen consumption, are often not feasible.

Oxygen consumption is a function of both supply and demand. The reduction in oxygen consumption could therefore be due to a decrease in supply or demand, or both. The possibility that a reduction in oxygen demand exceeds the reduction in supply is excluded in patients with shock by the presence of lactic acidosis. This indicates that tissue demands for

oxygen were greater than the supply, resulting in anaerobic metabolism.

A reduction in oxygen supply was indicated by the decrease in cardiac output and oxygen transport. Since the arterial oxygen concentration approximated normal value and the arteriovenous oxygen difference was increased, the reduction in oxygen transport and consumption are both attributable primarily to the reduction in cardiac output.

This interpretation of the basis for the reduction in oxygen consumption is consistent with the findings in patients without shock. In these patients cardiac output was only slightly reduced and the increase in oxygen extraction from arterial blood allowed for an equilibrium between oxygen supply and demand that was reflected by the normal values of both oxygen consumption and arterial lactate.

Compensatory Mechanisms for Reduced Oxygen Supply

The mechanisms by which a patient may compensate for a reduction in cardiac output include redistribution of blood flow and increased tissue extraction of oxygen.[20,21] Redistribution of blood flow probably occurred among patients with shock but was not specifically quantitated in our study. However, the extraction of oxygen was increased, as demonstrated by the arteriovenous oxygen difference, which exceeded 6 volumes percent, and the extraction ratios, which were greater than 30 percent. These findings are in contrast to data from studies on normal subjects in whom Reeves et al.[22] observed values for arteriovenous oxygen difference ranging from 3.5 to 4.5 volumes percent and from Parer et al.,[23] who documented extraction ratios averaging 21 percent.

P_{50} was characteristically increased in patients in whom acute myocardial infarction was followed by circulatory failure; these results parallel those of other investigators. Woodson et al.[24] and Metcalfe et al.[8] related the increase in P_{50} to reductions in cardiac output in patients with chronic heart failure. Shapell et al.[25] documented increases in P_{50} among patients in whom angina pectoris was induced by atrial pacing. Decreases in the affinity of the hemoglobin for oxygen also have been reported in human subjects after ascent to high altitudes.[26] Increases in P_{50} in patients with acute myocardial infarction recently reported by Kostuk et al.[9] were more pronounced among patients whose clinical course was complicated by heart failure. Since P_{50} was significantly increased in the majority of our patients with circulatory failure at the time of the initial measurements, a larger arteriovenous oxygen difference would be anticipated among such patients than in those without shock. However, this was not the case, indicating that factors other than the affinity of the hemoglobin for oxygen are involved in the extraction of oxygen at the tissue level. Among such factors, peripheral arteriovenous shunting, with part of the cardiac output bypassing ischemic areas, or reduced capability of the cells to take up oxygen, or both, might account for the unexpectedly high levels of mixed venous oxygen saturation observed among the patients with shock.

Quantitative Effect of Increased P_{50}

Our data demonstrate that the rightward shift of the oxyhemoglobin equilibrium curve would by itself provide an estimated 18 percent increase in oxygen availability. Whether this shift in the position of the curve will actually increase oxygen release by the same amount is contingent on the presence of additional factors such as peripheral shunting and the capability of the cells to take up oxygen at a given time.

The impact of an increase in P_{50} on the progression of circulatory failure may further depend on the time course of such changes. In the majority of the patients in this series, the highest P_{50} values were noted more than 24 hours after the onset of circulatory failure. Although significant increases in oxygen uptake followed increases in P_{50}, it is not as yet known whether this occurs rapidly enough to affect survival. Nevertheless, increases in P_{50} represent a potentially important compensatory mechanism when critical reductions in systemic flow limit survival after acute myocardial infarction. This mechanism may have added significance since oxygen availability is improved by the enhancement of oxygen release at the capillary level without augmenting the work load of the heart. In patients with acute myocardial infarction an increase in P_{50} also may be beneficial by increasing oxygen release to ischemic areas, thereby potentially reducing the size of the infarction.[27]

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Measurement of S-T Segment Elevation in Acute Myocardial Infarction in Man

Comparison of a Precordial Mapping Technique and the Frank Vector System

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Precordial S-T segment mapping has been used to evaluate the extent of ischemic injury in patients with acute myocardial infarction. Because precordial S-T segment mapping is time-consuming and is limited to patients with anterior wall myocardial infarction, we evaluated the possibility of using the magnitude (ST-VM) and direction (ST-VD) of the S-T vector, derived from X, Y and Z leads of the Frank vector system, as a substitute for the precordial S-T segment mapping technique.

Precordial S-T segment mapping and Frank system vectorcardiograms were simultaneously obtained in three groups: (1) nine normal subjects; (2) nine patients with persistent S-T segment elevation 2 to 15 months after acute anterior myocardial infarction; and (3) nine patients with acute anterior myocardial infarction studied on 41 occasions. For both systems the S-T segments were analyzed 20 and 60 msec after completion of inscription of the QRS complex. The sum of the S-T segment elevations for the 35 sites (ΣST) and the number of sites (NST) in which S-T segment elevations exceeded 0.1 mv were computed for the precordial S-T maps. The ST-VM and ST-VD were calculated by standard formulas from X, Y and Z lead tracings of the Frank vector system. Good correlations were observed between: ST-VM and ΣST ($r = +0.818$ and $+0.791$ at 20 and 60 msec, respectively, $P < 0.001$); and ST-VM and NST ($r = +0.773$ and $+0.705$ at 20 and 60 msec, respectively, $P < 0.001$). Furthermore, changes in the location of S-T segment elevations in serial precordial S-T segment maps were reflected by changes in ST-VD. Observations in patients with inferior wall myocardial infarction suggest that ST-VM and ST-VD can be serially followed in such patients. Thus, estimation of the magnitude and direction of the S-T vector is a simple alternative to standard precordial S-T segment mapping that allows for continuous monitoring of S-T segment elevations in all patients with acute myocardial infarction.

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The degree and extent of epicardial S-T segment elevation have been used to evaluate myocardial ischemic injury in animal experiments.[1–3] Maroko et al.[2] found a good correlation between epicardial S-T segment elevation and the extent of injury to the underlying myocardium, as determined by depression of myocardial creatine phosphokinase activity.[2]

Recently, precordial S-T segment mapping has been used in man to delineate alterations in myocardial ischemia,[4,5] examine the effects of therapy on the extent of myocardial ischemia[6] and detect exten-

TABLE I

Patient Groups Studied

Group	no. of Patients	Sex M	Sex F	Age (yr) (average and range)	no. of Studies
I (normal)	9	9	–	58 (39–62)	11
II (acute myocardial infarction)	11	9	2	60 (35–72)	43
III (persistent S-T elevation)	9	7	2	51 (32–66)	12
Totals	29	25	4		66

sions of myocardial infarction.[7] However, because the technique requires the recording and measurement of 35 to 72 separate electrocardiographic complexes, it is a laborious and time-consuming process. Furthermore, Maroko et al.[5] have stated that the technique should not be used in patients with inferior wall myocardial infarction.

We[8] have recently demonstrated that it is feasible to record the vectorcardiogram continuously in patients with acute myocardial infarction. In view of the aforementioned limitations of precordial S-T segment mapping, we evaluated the possibility of using the magnitude and direction of the S-T segment vector as a substitute for the precordial S-T segment mapping technique.[8a]

Methods

Patient Groups

We studied 29 patients classified into three groups (Table I). Group I (normal subjects) consisted of nine men who had no history of cardiovascular disease and who had a normal cardiac examination and 12 lead electrocardiogram. Group II (acute myocardial infarction) consisted of 11 patients who had clinical, enzymatic and electrocardiographic evidence of acute myocardial infarction. Nine of the 11 had anterior wall infarction by electrocardiographic criteria and 2 had inferior wall infarction. The latter two are discussed separately; they were not included in the statistical analysis because of the limitations of precordial S-T mapping in inferior wall infarction. Group III consisted of 9 patients who had had an acute myocardial infarction 2 to 15 months previously and who had persistent S-T elevation in the precordial leads of the 12 lead electrocardiogram. Sixty-six studies were performed in the 29 patients (Table I). The small number of women (4 of 29) is due to difficulties in accurate placement of precordial electrodes in these patients.

Data Collection

Precordial S-T segment mapping: A "chest blanket" with 35 holes (2 cm in diameter) was constructed of thin sheet rubber. The 35 holes were placed in a 5 by 7 grid; the 5 horizontal holes were designated by the letters A (top) to E (bottom), and the 7 vertical columns were numbered from 1 (patient's right) to 7 (patient's left). The holes were spaced according to the method of Maroko et al.[5] The chest blanket was taped on the patient's chest with the top right hole (A1) placed in the second intercostal space at the right parasternal line, and the bottom left hole (E7) at or close to the sixth intercostal space in the left midaxillary line. With subjects in the supine position, a pediatric size chest electrode (Welsh electrode, Bowen and Co., Bethesda, Md.) was sequentially applied to the chest wall through the 35 holes, using an electrode paste (Redux Creme, Hewlett-Packard Corp., Palo Alto, Calif.) Several complexes were recorded at each point on a standard electrocardiograph (Cardi-O-Mite, model S-200, Bendix Corp., Rochester, N. Y.) at a paper speed of 25 mm/sec and a standardization of 1 mv/10 mm.

Frank system X, Y and Z lead recording: While the precordial S-T segment map was being recorded, a continuous recording of the X, Y and Z leads was made, using the technique previously described.[8] In this technique, the Frank X, Y and Z leads are continuously monitored and recorded on a strip chart recorder. Eight disposable electrodes are applied to the patient according to the Frank lead system,[9] with five electrodes on the thorax, one electrode on the back of the neck and one electrode on each leg. A special resistor network transforms the information from the leads into the conventional Frank X, Y and Z signals. These signals (corresponding roughly to leads I, aVF and V_1, respectively, of the routine 12 lead electrocardiogram) are routinely displayed at the patient's bedside and at the nursing station. When permanent records are desired (as in this study, for example), the X, Y and Z leads are recorded at a paper speed of 100 mm/sec with a standardization of either 20 or 40 mm/mv on a pressurized ink direct recorder (Brush Mark 880, Gould Corp., Cleveland, Ohio). Representative tracings are shown in Figure 1. We[8] have previously found excellent agreement between vectorcardiographic loops obtained with a standard commercial vectorcardiograph (Hewlett-Packard, model 1507A) and those obtained by plotting our Frank X, Y and Z leads against one another. We routinely use one or more of the Frank system signals instead of the usual single lead system to monitor the rhythm of patients in our myocardial infarction research unit.[8]

Tracing analysis: In all tracings, the isoelectric base line was determined by drawing a straight line between P-R segments of adjacent beats. All measurements were made with reference to this isoelectric line and were recorded in millivolts. The termination of the QRS complex was visually determined for each beat, and the S-T elevation 20 and 60 msec after termination of the QRS inscription were recorded for the 35 precordial leads and the X, Y and Z leads (Fig. 1). The sum of S-T elevations (in millivolts) for the 35 precordial sites was computed and termed ΣST. The number of sites in which S-T segment elevation exceeded 0.1 mv was also computed and termed NST.[5]

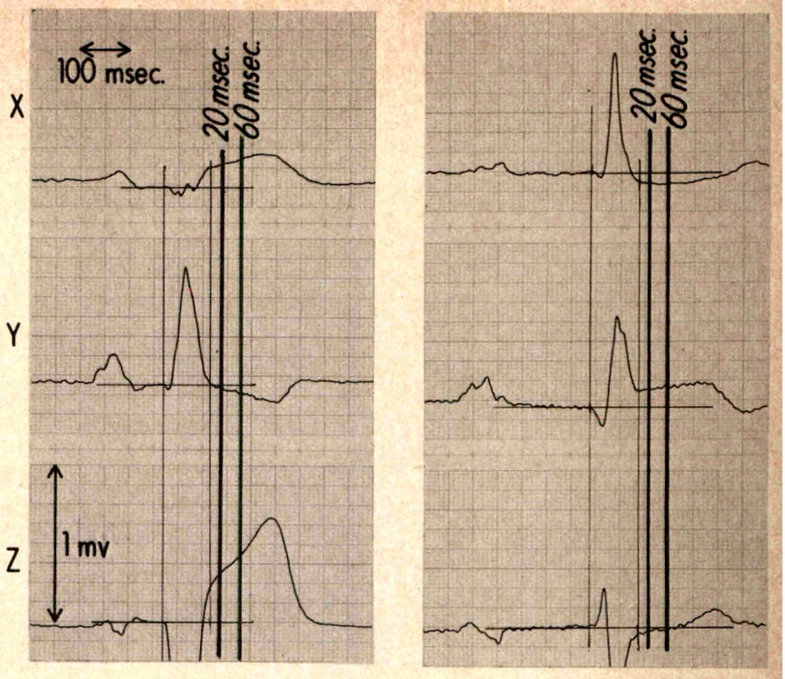
Calculation of the S-T segment vector: The magnitude, azimuth and elevation of the S-T vector were calculated using the following standard formulas:

$$\text{Magnitude (ST-VM)} = \sqrt{X^2 + Y^2 + Z^2}$$

$$\text{Azimuth (ST-AZ)} = \tan^{-1}\frac{Z}{X}$$

$$\text{Elevation (ST-EL)} = \tan^{-1}\frac{Y}{\sqrt{X^2 + Z^2}}$$

Magnitude is expressed in millivolts, and azimuth and elevation are expressed in degrees. We chose a reference system in which 0° azimuth is to the patient's left, 90° azi-



Acute Anterior Myocardial Infarction

	20 msec.	60 msec.
X	+0.15 mv	+0.175 mv
Y	-0.025 mv	-0.05 mv
Z	+0.30 mV	+0.425 mv
ST-VM	+0.34 mv	+0.46 mv
Azimuth	+63°	+68°
Elevation	-4°	-6°

Acute Inferior Myocardial Infarction

	20 msec.	60 msec.
X	-0.05 mv	-0.075 mv
Y	+0.125 mv	+0.125 mv
Z	-0.025 mv	0.0 mv
ST-VM	+0.14 mv	+0.15 mv
Azimuth	+207°	+180°
Elevation	+66°	+59°

FIGURE 1. Representative Frank system X, Y and Z lead recordings in two patients with anterior **(left)** and inferior **(right)** wall myocardial infarction. The beginning and end of the QRS complex are indicated by the lighter vertical lines. Measurements were made 20 and 60 msec after QRS inscription, as indicated by the darker vertical lines. Below are shown the measured values (in millivolts) for each lead, as well as the calculated magnitude (ST-VM), azimuth and elevation for the S-T segment. In the X and Y leads, positive forces are upward, but this orientation has been reversed in the Z lead to aid orientation with the standard 12 lead electrocardiogram.

muth is anterior to the patient, 180° is to the patient's right and 270° is posterior to the patient. With respect to elevation, −90° is at the patient's head, 0° at the horizontal plane through the heart and +90° at the patient's feet.

Reproducibility and variability of the techniques: To test reproducibility of the techniques, simultaneous precordial mapping and Frank X, Y and Z recordings were made on two occasions, less than 30 minutes apart, in each of six patients in stable condition. Tracings for both tests were analyzed by the same person. Paired t test analysis revealed that there was no difference between the two recordings with respect to the ST-VM, ΣST or NST at 20 or 60 msec after QRS inscription. Because the tracings were analyzed by more than one person, on eight occasions the same tracings were analyzed independently by two observers to test variation among observers. No systematic differences were noted, and the maximal difference between the two observers was 13 percent (for ΣST at 60 msec after QRS inscription).

Data analysis: All data were punched onto cards, and analysis was performed on a digital computer (XDS Sigma 3). Standard statistical techniques were used to calculate correlation coefficients, regression equations and results of paired and unpaired t tests.[10]

Results

Correlation between ΣST and NST of precordial S-T mapping and ST-VM of the Frank X, Y and Z lead recordings: Data from 51 observations* of simultaneous precordial S-T mapping and the Frank X, Y and Z lead recordings are compared in Figures 2 and 3. Data from all three patient groups are included. Figure 2 demonstrates that there is a moderately strong correlation between the ST-VM and ΣST 20 and 60 msec after completion of the QRS complex inscription. Correlations were equally strong for both men and women (r = +0.871 and +0.865 for men and women, respectively, 20 msec after inscription). Figure 3 demonstrates that there is also a good correlation between ST-VM and NST at both times after QRS inscription. Again, correlations were equally good for both men and women (r = +0.781

* Data from 15 observations (2 in patients with inferior wall myocardial infarction, 6 from reproducibility tests and 7 from variability tests) were not included in the analysis of correlation between the two techniques.

and +0.842, respectively, at 20 msec). Since we found no systematic differences between the data obtained 20 and 60 msec after completion of QRS inscription, the subsequent results will refer only to data obtained 20 msec after inscription.

To show the correlation between the two techniques in individual patients, results of several simultaneous studies from two patients are compared in Figure 4. In both patients, significant changes in ΣST occurred during their clinical course, and these changes were reflected by concordant changes in ST-VM.

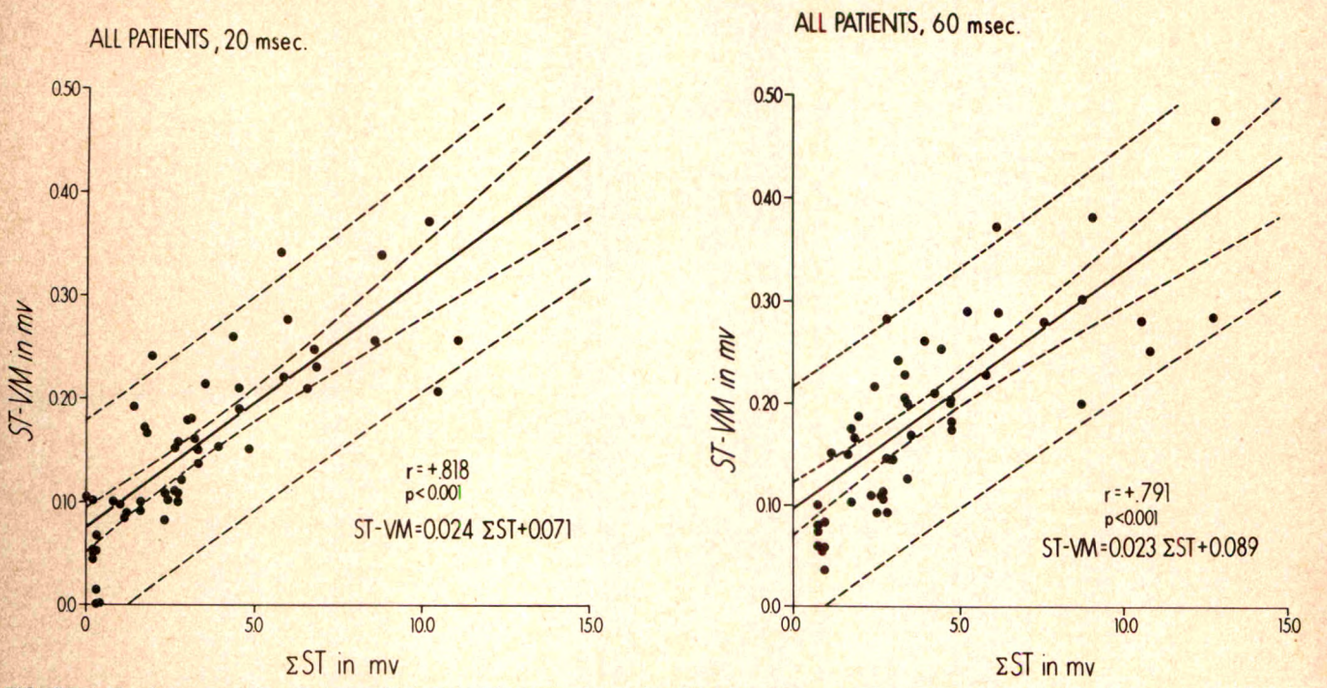


FIGURE 2. The S-T segment vector magnitude (ST-VM) obtained from Frank system X, Y and Z lead recordings is plotted against the sum of the 35 S-T segments (ΣST) obtained by chest wall mapping. The data, obtained 20 **(left)** and 60 **(right)** msec after completion of the QRS complex, are from all groups studied. Correlation coefficients and the regression equations are shown. The **solid line** is the regression line, the **inner dashed lines** are the confidence bands for the regression lines, and the **outer dashed lines** are the prediction bands.

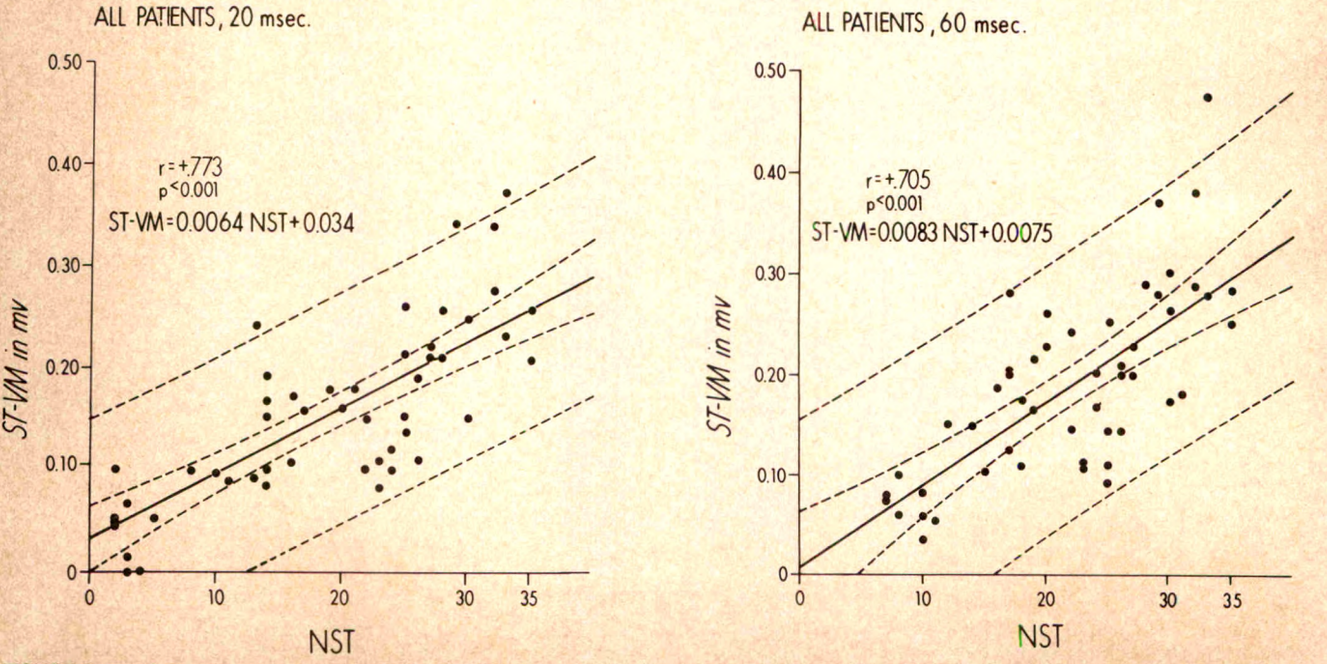


FIGURE 3. The S-T segment vector magnitude (ST-VM) obtained from Frank system X, Y and Z lead recordings is plotted against the number of sites (NST) on precordial S-T segment maps that exceeded 0.1 mv. Data, obtained 20 and 60 msec after completion of the QRS complex, are from all groups studied. Other notation as in Figure 2.

Correlation of changes in the distribution of S-T elevations in precordial mapping and the S-T vector direction: We also attempted to correlate the distribution of S-T segment elevations, as determined by S-T segment mapping, with the S-T vector direction, as determined from the Frank X, Y and Z recordings. Thus, in addition to ST-VM, the azimuth (ST-AZ) and elevation (ST-EL) of the S-T segment were calculated for each set of X, Y and Z lead tracings. Figure 5 shows serial data from S-T mapping and Frank leads in a patient with an anterior wall myocardial infarction. Peak voltages occurred in columns 2 and 3 of the chest mapping throughout the patient's course, and this was reflected by the S-T vector azimuth, which remained within a narrow range of 78° to 90°, whereas S-T vector elevation did not change significantly.

In contrast to Figure 5, from a patient in whom the precordial location of S-T segment elevations did not change, the data in Figure 6 are from a patient with

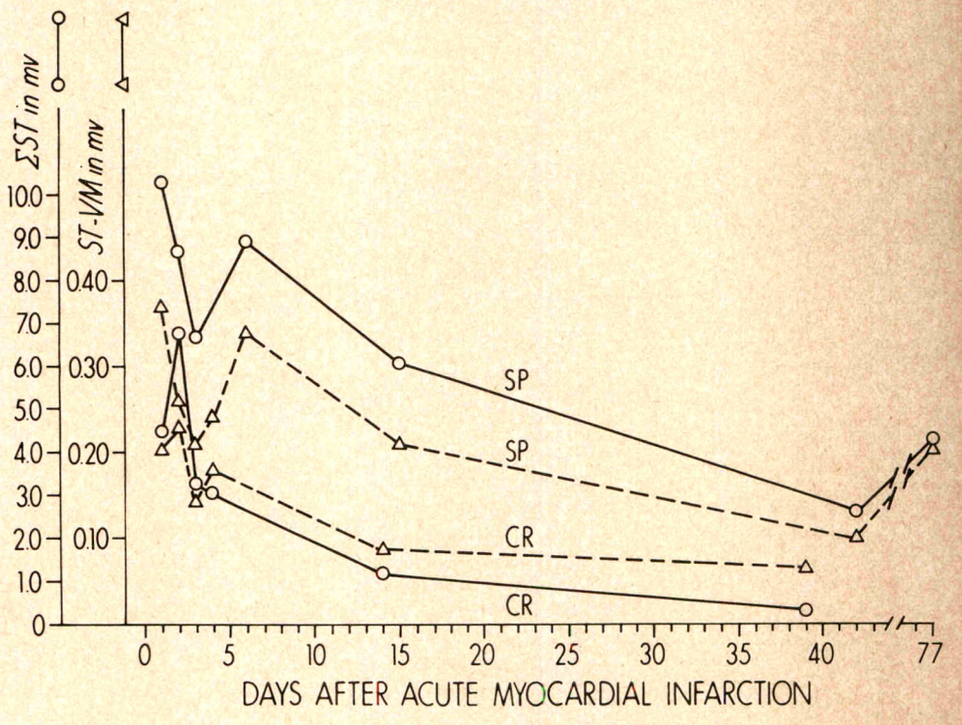


FIGURE 4. Serial data for ST-VM (Δ) and ΣST (O) in two patients (CR and SP) are shown. Note the close correlation between the changes calculated by the two techniques.

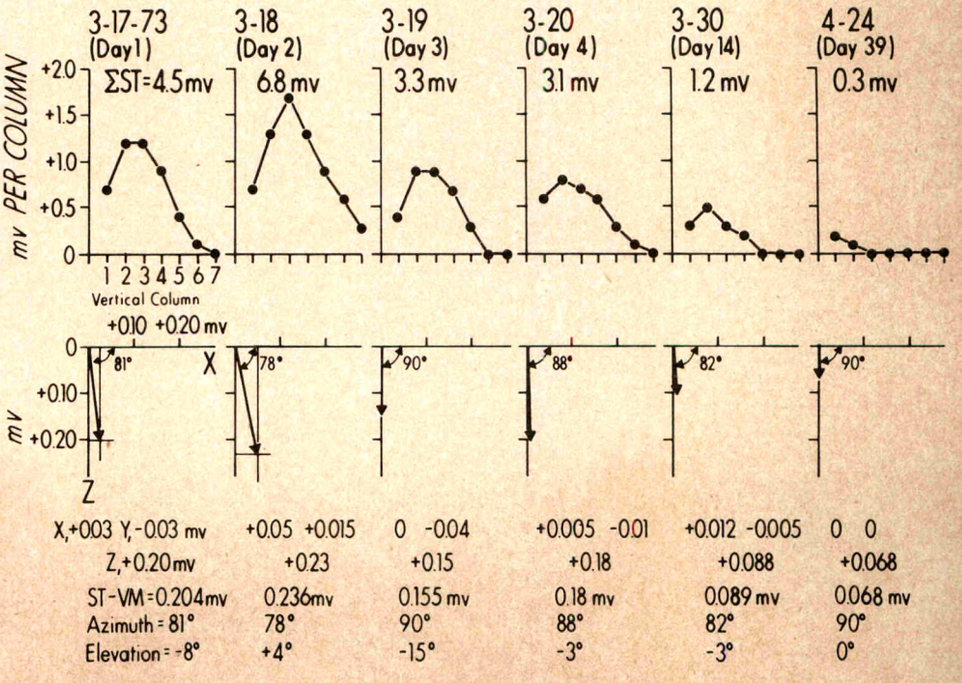


FIGURE 5. Serial data are shown for precordial S-T mapping **(upper row)** and Frank X, Y and Z lead recordings **(lower row)** in a patient with anterior myocardial infarction. In each panel of the upper row, the sum (in millivolts) of the S-T segments for each S-T mapping vertical column is plotted. For example, the sum of S-T elevations on day 1 in vertical column 1 (the most rightward column on the patient's chest) was 0.7 mv. On the same day, the sum in vertical column 4 was 0.9 mv. In the Frank leads recorded at the same time **(lower row)**, the S-T elevation was 0.2 mv in lead Z and 0.03 mv in lead X. Plotting of these data reveals a vector magnitude of 0.204 mv and an azimuth of 81° in the horizontal plane. Notation as in Figure 1.

anterior wall infarction who manifested significant changes in the distribution of S-T elevation on S-T mapping. Peak voltage shifted from column 3 to column 5 on the 5th hospital day, when clinical signs of pericarditis developed. This was reflected in the Frank leads by a significant shift in S-T azimuth from 60° to 17°, with only a slight change in S-T vector elevation (Fig. 6). With clinical resolution of the pericarditis 2 weeks later, peak voltage on S-T mapping shifted back to column 3, and S-T vector azimuth returned to the previous direction as well. Thus, shifts in the distribution of S-T elevations as measured by precordial mapping are simultaneously reflected by changes in S-T elevation and azimuth, as measured by Frank X, Y and Z leads.

Validity of Frank X, Y and Z system in inferior wall myocardial infarction: Data from a patient with an inferior wall myocardial infarction are shown

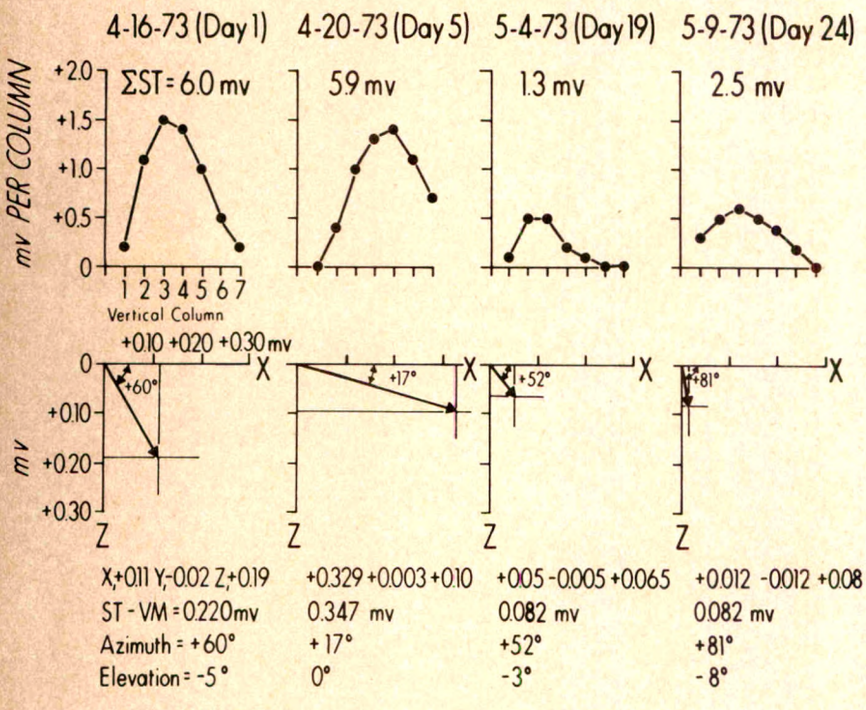


FIGURE 6. Serial data are shown for precordial S-T mapping **(upper row)** and Frank X, Y and Z lead recordings **(lower row)** in a patient with anterior wall infarction who manifested significant changes in the distribution of S-T segment elevations on the 5th hospital day. Both techniques reflect shifts in distribution and direction of S-T elevation. See text for explanation. Notation as in Figures 1 and 5.

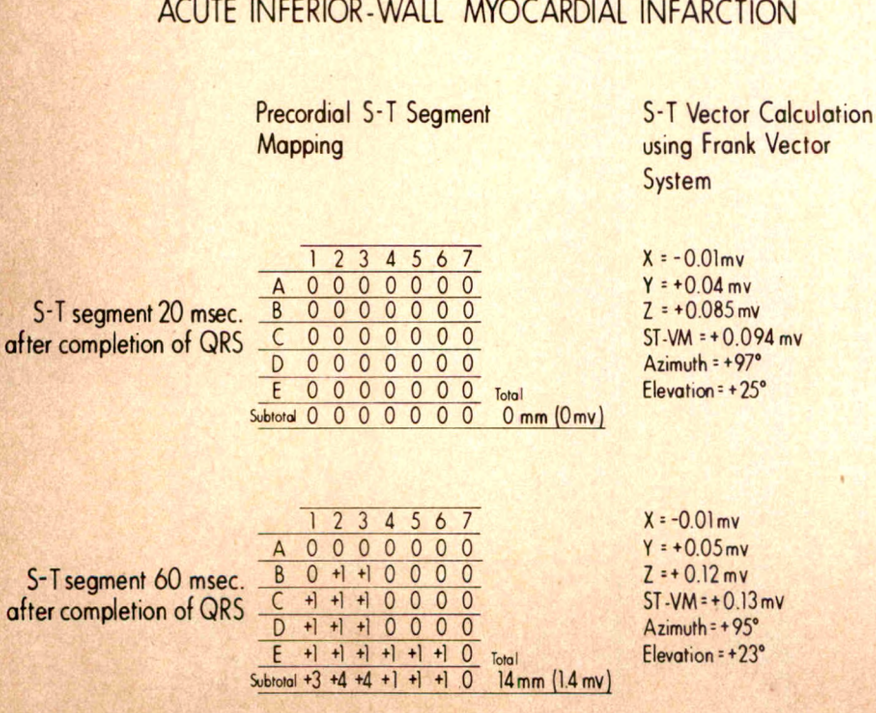


FIGURE 7. Comparison of S-T segment mapping **(left)** and Frank X, Y and Z leads **(right)** in a patient with inferior wall acute myocardial infarction. Values (in millimeters) for each of the 35 precordial sites are shown for both 20 and 60 msec after completion of the QRS complex. Other notation as in Figure 1.

in Figure 7. Precordial S-T segment mapping revealed no S-T elevations 20 msec after QRS inscription, and only minimal S-T elevations 60 msec after QRS inscription. However, the extent and location of S-T elevation were reflected in the simultaneously recorded Frank X, Y and Z leads. The magnitude of the S-T vector was 0.094 mv 20 msec after QRS inscription, and the inferior location of the infarct was reflected by an S-T vector elevation of +25°.

Utility of Frank X, Y and Z leads for serial studies: Because the Frank X, Y and Z leads can be continuously recorded, the magnitude and direction of the S-T segment vector can be easily determined at any time without disturbing the patient. An example of the utility of the technique is shown in Figure 8. In this patient, who had an inferior wall infarction, the Frank leads were continuously recorded on a frequency modulation analog tape recorder (Honeywell 7600, Honeywell Corp., Denver, Colo.). At a later time, strip chart recordings were made of the leads at significant periods in the patient's course, and S-T vector magnitude, azimuth and elevation were calculated. On admission, the patient had third-degree atrioventricular (A-V) block, and the S-T magnitude was at a maximal value. Subsequently, 16 other calculations of vector magnitude were made over a 48 hour period, without disturbing the patient at any time. Intermediate levels of vector magnitude were noted when the patient had second degree block of the Wenckebach type. A direct correlation was noted between the S-T vector magnitude and the P-R interval when the patient had first degree A-V heart block ($r = +0.90$, $P < 0.001$). Although the data suggest that in this patient there was a direct relation between myocardial ischemia and the extent of A-V heart block, no conclusions should be drawn from this single study. These data are shown merely to illustrate the flexibility and utility of this technique.

Discussion

The amount of S-T segment elevation in a QRS-T complex is thought to correlate with myocardial ischemia. In 1949, Wegria et al.[1] showed that epicardial S-T segment elevation in dogs correlated well with induced reductions in coronary blood flow. More recently, Maroko et al.[2] recorded epicardial electrocardiograms on the anterior surface of the left ventricle in the distribution and vicinity of an occluded branch of the left anterior descending coronary artery. They found that elevation of the S-T segment accurately reflected the severity and extent of myocardial ischemic injury. In other canine experiments,[5] the same group demonstrated good correlations between myocardial ischemia and S-T segment elevations recorded from the chest surface.

Several recent studies have documented the clinical usefulness of quantitating S-T segment elevation in precordial electrocardiographic leads. Pelides et al.[6] and Maroko et al.[5] showed the value of precordial S-T segment mapping in delineating alterations in myocardial ischemia and in examining the effect of therapy on the extent of ischemia in patients with myocardial infarction. Reid et al.[7] found such mapping useful in detecting extensions of myocardial infarction, some of which were not detected by routine 12 lead electrocardiogram. Nielsen[11] and Wilson and Pantridge[12] found that the magnitude of S-T elevation gave valuable prognostic information that was useful in selecting patients for prolonged monitoring.

In light of these findings, we believed that evaluation of the S-T segment would be a useful clinical and research tool. However, because precordial S-T segment mapping is a relatively time-consuming and laborious procedure, we examined the possibility of using determination of the magnitude and direction of the S-T vector in the Frank system vectorcardiogram as a substitute technique. Our data reveal that

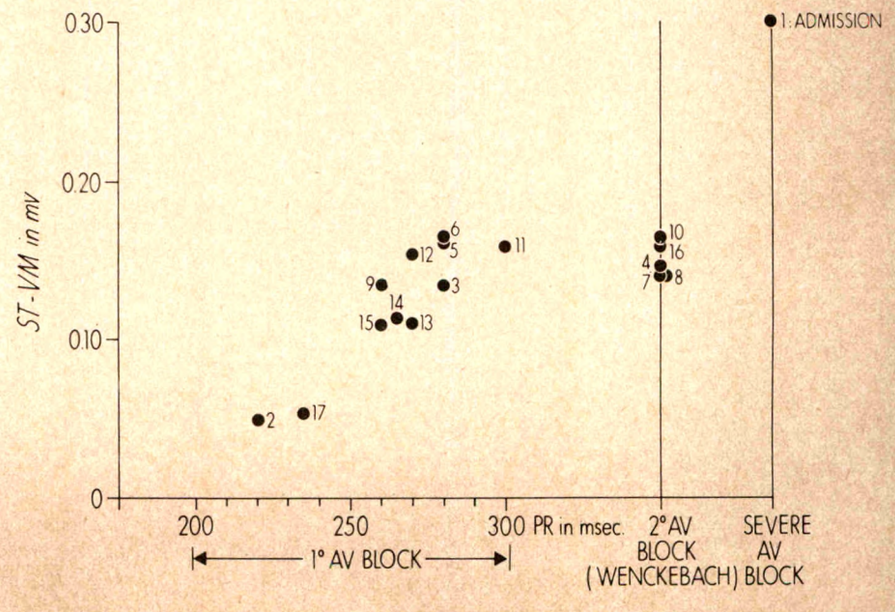


FIGURE 8. Relation between the severity of A-V block and serial S-T vector magnitudes (ST-V-M) in a 51 year old man with an inferior wall myocardial infarction. The numbers refer to the chronologic order in which the data were gathered, from 1 (admission) to 17 (48 hours after admission). When the patient had first-degree A-V block, there was a strong correlation between the P-R interval and ST-VM ($r = +0.90$, $P < 0.001$). AV = atrioventricular; PR = P-R interval.

the technique is a reasonable substitute, and that the data obtained have a moderately strong positive correlation with those obtained from S-T segment maps recorded by usual methods. The method is feasible in patients with acute inferior wall infarction (Fig. 7), and can also be used for multiple serial studies (Fig. 8). In addition, since the magnitude and direction of the S-T segment are calculated on a single beat (using the three simultaneously recorded leads), even beat to beat changes in S-T segment elevation can be evaluated. This latter feature should be helpful in evaluating the time course of interventions such as nitroglycerin that might be expected to rapidly affect myocardial ischemia. Furthermore, the method reflects changes in direction in the S-T segment (Fig. 5 and 6). In view of these advantages, the technique should be useful for monitoring the S-T segment in clinical and research studies.

Causes of variations in the two techniques: In comparing data from our technique with data obtained using S-T segment mapping, we noted correlation coefficients in the range of 0.8 (Fig. 2 and 3), indicating that approximately 64 percent (0.8^2) of the variation in our technique could be explained by variation in the standard S-T segment mapping technique.[13] Causes for the other 36 percent of the variation may include the following: (1) *Experimental error,* including measurement error (different standardizations and paper speeds were used in the two techniques) as well as errors in recording and placement of electrodes. (2) *Assumption of a single cardiac dipole.* Vectorcardiography (and thus our technique) assumes a single cardiac dipole, whereas S-T segment mapping, utilizing individual body surface recordings, does not. On the basis of recently reported studies,[14,15] we believe that this source of error probably accounts for less than 15 percent of differences. (3) *Errors due to infarct location.* Our technique is influenced by all changes in the S-T segment, whereas S-T segment mapping is influenced mostly by those changes that occur in the area being mapped. Thus, an anterolateral myocardial infarction might produce S-T segment elevation over parts of the chest wall not being mapped; this event would presumably be reflected by our technique, but not, of course, by S-T segment mapping, and would thus contribute to the variation noted in Figures 2 and 3.

Clinical implication: We used continuous recordings of Frank X, Y and Z leads to calculate the magnitude and direction of the S-T segment in normal people and in patients with new and old myocardial infarction. The data thus obtained were compared with data obtained from standard precordial S-T segment mapping techniques, and moderately strong correlations were found between the two approaches. The Frank technique is simple, easy to use and useful in all locations of myocardial infarction. It should prove useful in clinical and research studies in patients with myocardial infarction.

Acknowledgment

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Reappearance of Anterior QRS Forces After Coronary Bypass Surgery

An Electrovectorcardiographic Study

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This report describes the reappearance of anterior QRS electrical forces in six patients after direct coronary arterial bypass surgery. Each patient had severe coronary artery disease including a segmental stenosis of the left anterior descending artery. Revascularization was performed by direct anastomosis of the left internal mammary artery to the left anterior descending coronary artery and saphenous vein bypass of other stenotic coronary arteries. Preoperative electrocardiograms and vectorcardiograms showed patterns of anterior wall myocardial infarction with absent or diminutive anterior QRS forces. In each case, postoperative studies demonstrated the regeneration of anterior QRS forces within 10 days of operation. Although these patients represent a small percent of those with a preoperative pattern of infarction who undergo coronary revascularization, the findings demonstrate that electrically silent areas of myocardium may be altered and are not always synonymous with myocardial cell death. Chronic myocardial ischemia may in certain instances produce electrocardiographic and vectorcardiographic patterns of myocardial infarction that may be reversible upon reestablishment of perfusion to ischemic areas.

Vectorcardiography has become a useful adjunct in the pre- and postoperative evaluation of patients undergoing coronary arterial surgery and in conjunction with standard electrocardiography has been used to assess the incidence of perioperative myocardial infarction.[1,2]

In the study described here, vectorcardiography demonstrated early after direct coronary arterial bypass surgery abolition of the preoperative pattern of anterior wall myocardial infarction. Although previous reports[3,4] have shown that Q waves in standard electrocardiograms may be transient and are not always associated with irreversible myocardial damage, the reversible nature of electrically silent areas of myocardium[3] has not previously been documented after coronary bypass surgery or corroborated by vectorcardiography.

This report describes six patients with obstructive coronary artery disease, including severe proximal segmental stenotic lesions in the left anterior descending artery, who underwent direct coronary bypass surgery. Preoperative electrocardiograms and vectorcardiograms showed patterns of anterior wall myocardial infarction with absent or diminutive anterior QRS forces. In each instance, postoperative studies demonstrated the reappearance of more normal anterior forces within 10 days of operation. Specific examples are shown and the implications of these observations discussed.

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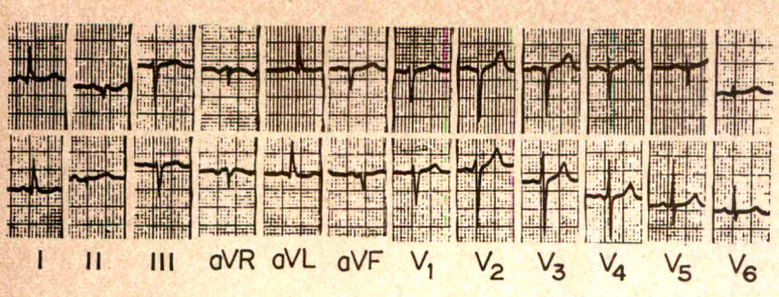

FIGURE 1. Case 2. The preoperative electrocardiogram **(top)** shows a pattern of anterior wall myocardial infarction with Q waves in leads V_2 and V_3 and "poor R wave progression" across the precordium. The postoperative record **(bottom)** demonstrates reappearance of normal R wave progression and loss of the pattern of anterior infarction. Left anterior hemiblock is evident in both the pre- and postoperative tracings.

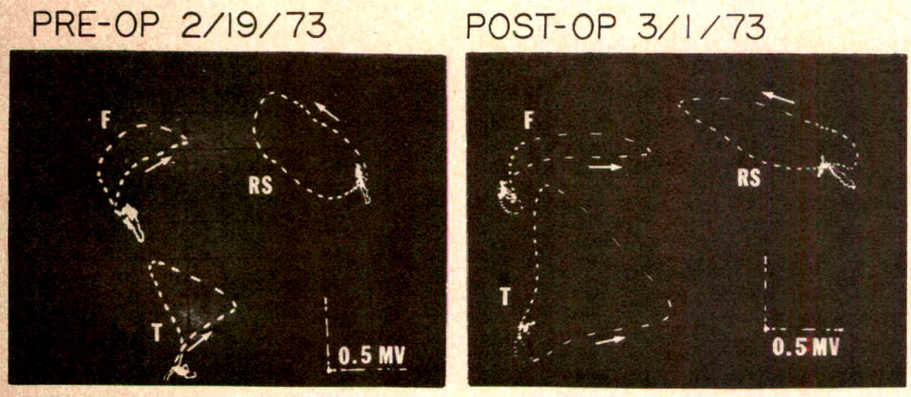

FIGURE 2. Case 2. Vectorcardiograms before **(left)** and after **(right)** operation, in the frontal (F), right sagittal (RS) and transverse (T) planes. The interval between dashes is 2.5 msec. The preoperative tracings show a pattern of anterior wall infarction with the 20 msec vector posterior to the null point. The postoperative tracings demonstrate regeneration of anterior QRS forces, best visualized in the transverse plane. Inferior wall myocardial infarction and left anterior hemiblock are evident in both tracings.

TABLE I

Clinical Characteristics

Case no.	Age (yr) & Sex	Angina	Past MI	Arrhythmia
1	42M	Yes	Yes	No
2	43M	Unstable	No	No
3	57M	Unstable	No	PVCs
4	44M	Unstable	No	No
5	56M	Yes	No	No
6	55M	Yes	Yes	No

MI = myocardial infarction; PVCs = premature ventricular contractions.

TABLE II

Cardiac Catheterization Findings

Case no.	LV-EDP (mm Hg)	LV Asynergy		Coronary Arterial Stenosis		
		Anterior	Posterior	LAD >90%	LCx >75%	RCA >75%
1	12	Hypokinesis	Akinesis	Yes	Yes	Total
2	10	Hypokinesis	Normal	Total	Yes	No
3	10	Hypokinesis	Hypokineses	Yes	No	Yes
4	9	Normal	Normal	Yes	Yes	Yes
5	8	Hypokinesis	Normal	Total	Total	No
6	14	Normal	Normal	Total	Yes	No

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricular; LV-EDP = left ventricular end-diastolic pressure; RCA = right coronary artery.

Methods

Pertinent clinical characteristics of the six patients are summarized in Table I. All patients were symptomatic with angina pectoris. Three patients had rapidly progressive symptoms and an unstable anginal pattern; two had a clinical history of a previous myocardial infarction. In all six patients preoperative electrocardiograms showed a pattern of anterior wall myocardial infarction with Q waves in the precordial leads. In two patients (Cases 1 and 2), electrocardiograms showed associated patterns of inferior wall infarction. The six patients represent approximately 1 percent of all patients with preoperative electrocardiographic and vectorcardiographic patterns of myocardial infarction who underwent direct coronary arterial surgery at our institution between January 1973 and June 1974.

Vectorcardiograms, recorded on a Hewlett-Packard vector programmer using the Frank lead system, were obtained in the transverse, right sagittal and frontal planes at 0.5 and 0.2 mv standardizations. They were recorded within 3 days before the coronary bypass procedure and again within 10 days after the procedure. Standard 12 lead electrocardiograms were recorded on the same day as the vectorcardiograms.

Vectorcardiographic criteria for an anterior or anteroseptal myocardial infarction, as outlined by Benchimol,[5] were present in each patient preoperatively. In the transverse plane, the 20 msec QRS vector was directed posteriorly and to the left. The rotation of the main body of the QRS loop in the transverse plane was counterclockwise. The posterior position of the 20 msec QRS vector was confirmed in the sagittal plane. Vectorcardiographic criteria for inferior wall infarction[5] were present in three patients (Cases 1 to 3) with the 25 msec QRS vector being superior to the null point in the frontal and sagittal planes in these cases.

Right and left heart catheterization, ventriculography in the right anterior oblique projection and selective coronary arteriography in multiple oblique views were performed by standard techniques. Table II summarizes the

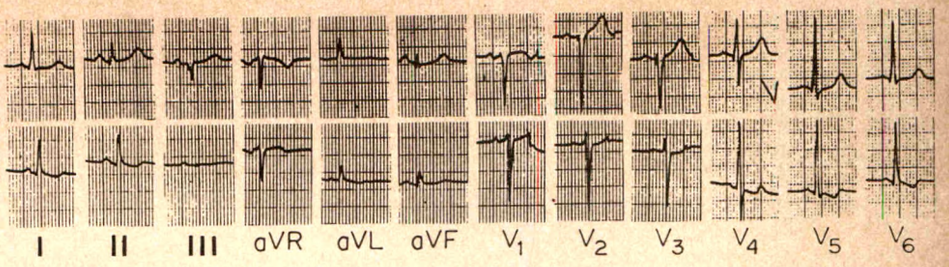

FIGURE 3. Case 3. The preoperative electrocardiogram **(top)** shows Q waves and diminutive R waves in leads V_1 through V_3. In the postoperative tracing, **(bottom)** the Q waves in the right precordial leads have disappeared and more normal R wave progression is evident.

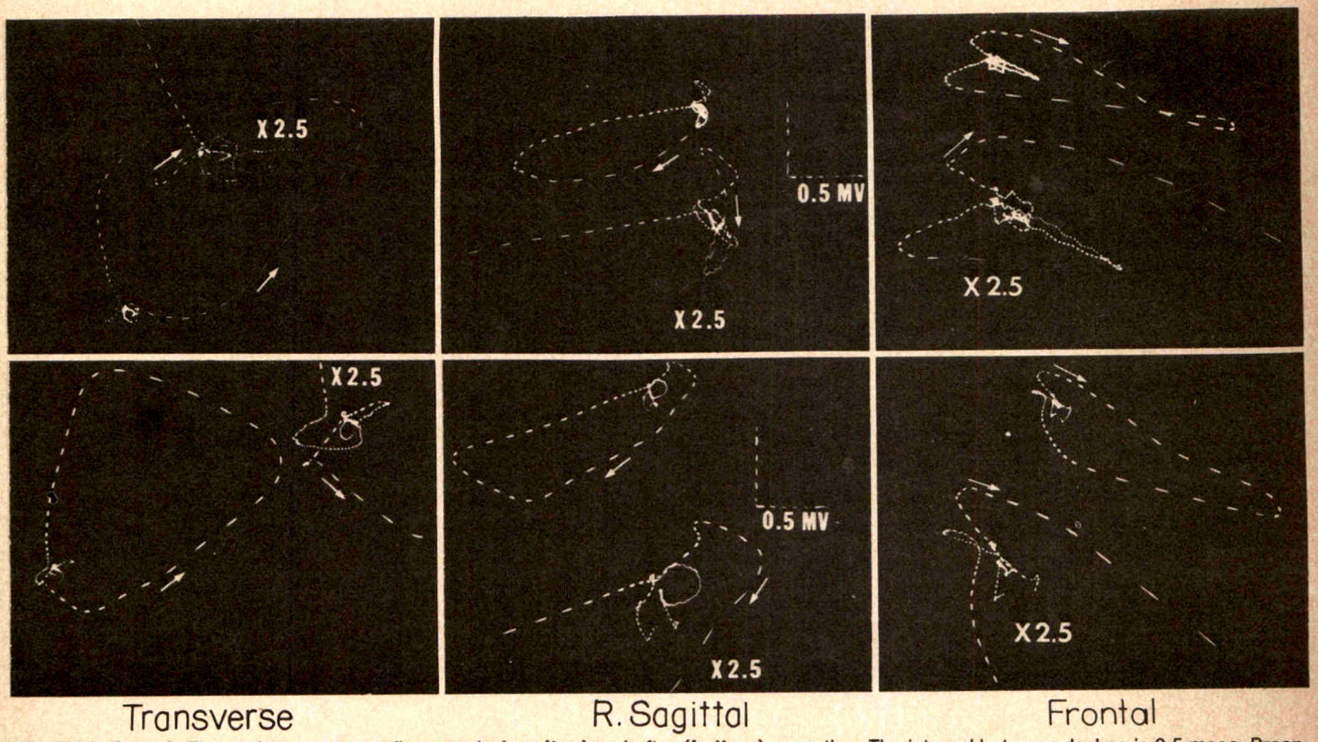

FIGURE 4. Case 3. Three-plane vectorcardiograms before **(top)** and after **(bottom)** operation. The interval between dashes is 2.5 msec. Preoperatively, there are patterns of anterior and inferior wall infarction. In the transverse plane the 20 msec vector is posterior to the null point. The postoperative tracings show augmentation of the anterior QRS forces, best seen in in the transverse plane. The abnormal superior direction of the initial forces is less marked postoperatively (right sagittal plane). Abnormal slowing of the initial and terminal forces is present in both the pre- and postoperative tracings.

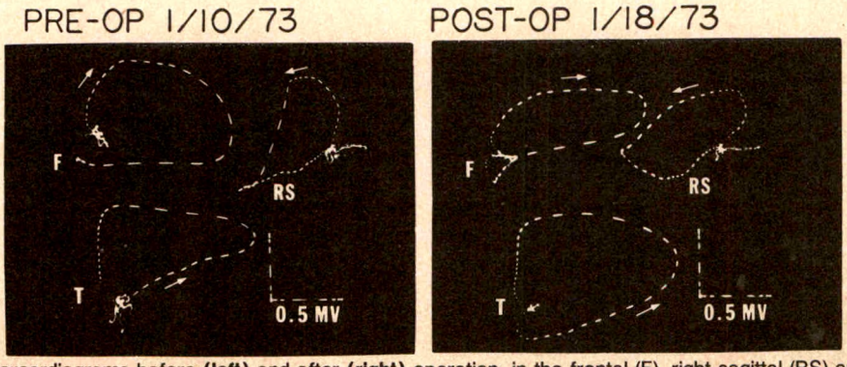

FIGURE 5. Case 1. Vectorcardiograms before **(left)** and after **(right)** operation, in the frontal (F), right sagittal (RS) and transverse (T) planes. The interval between dashes is 2.5 msec. In the preoperative record, the initial forces are clearly abnormal with the 20 msec vector posterior to the null point. Postoperatively, there has been regeneration of anterior QRS forces, best seen in the transverse plane. Both tracings demonstrate changes of an inferior wall myocardial infarction and superiorly directed forces (left axis deviation). Abnormal slowing of the initial and terminal forces is present in both the pre- and postoperative tracings.

pertinent cardiac catheterization findings. Right heart and pulmonary arterial pressures and resting values for cardiac output were normal in all patients. The left ventricular end-diastolic pressure at rest was normal in five patients and slightly increased in one patient (Case 6). Right anterior oblique ventriculograms revealed moderate to severe hypokinesia of the middle or distal anterior wall segments in four patients; abnormalities of contractility in the posteroinferior wall of the left ventricle were noted in two. Two patients (Cases 4 and 6) had normal preoperative ventriculograms.

Selective coronary arteriograms demonstrated severe proximal obstructive lesions in the left anterior descending coronary artery in all six patients. Triple vessel coronary disease was seen in two patients; three had severe disease of the right coronary artery.

All six patients underwent coronary arterial bypass surgery[6,7] with direct bypass of the severely stenosed left anterior descending coronary artery using the left internal mammary artery.[6] In two patients, vein bypass grafts to large anterior diagonal branches were also performed. In addition, vein bypass grafts were performed to major branches of the circumflex system in five patients and to the right coronary artery in two patients. Five of the six patients had multiple bypass grafts.

Results

Preoperative: All electrocardiograms showed typical patterns of transmural anterior wall myocardial infarction with Q waves in the right precordial leads. Postoperatively, in each instance, there was regeneration of R waves in these leads and loss of the pattern of definite infarction. Preoperative vectorcardiograms of the QRS loop showed abnormal initial forces compatible with an anterior wall myocardial infarction. In each case, the transverse and right sagittal planes showed the 20 msec QRS vector posterior to the null point.

Postoperative: Vectorcardiograms after operation showed return of normal initial anterior forces and loss of the preoperative pattern of anterior wall infarction. Postoperative transverse plane vectorcardiograms showed early initial forces to be rightward and anterior and the 20 msec QRS vector leftward and anterior to the null point. Pre- and postoperative scalar electrocardiograms and three-plane vectorcardiograms from two patients (Cases 2 and 3) are illustrated in Figures 1 to 4. Pre- and postoperative vectorcardiograms from Patient 1 are illustrated in Figure 5.

Postoperative vectorcardiograms demonstrated regeneration of anterior QRS forces without a significant change in the frontal plane QRS axis (Fig. 2, 4 and 5). Although left axis deviation was evident in the preoperative tracings (Fig. 2 and 5), it persisted in the postoperative vectorcardiograms. The lack of significant change in the frontal plane QRS axis precludes the possibility that improved conduction in the left anterior fascicle postoperatively or damage to the left posterior fascicle at operation caused the reappearance of anterior QRS forces in the sagittal and transverse plane vectorcardiograms. The slowing of the initial QRS forces, present in the preoperative vectorcardiograms of all six patients (Fig. 2, 4 and 5), might suggest that the abnormal posteriorly directed QRS forces were the result of aberrant ventricular conduction, but the persistence of slow initial QRS forces despite their more normal anterior direction postoperatively provides evidence against this suggestion. However, one cannot exclude with certainty the possibility that the postoperative vectorcardiograms represented a different form of aberrancy rather than normalization of the preoperative tracings.

Follow-up: All six patients have been free of symptoms of angina pectoris 3 to 18 months postoperatively. Two patients underwent cardiac catheterization 2 weeks and 3 months, respectively, after operation. In both cases, the left internal mammary artery bypass graft to the left anterior descending coronary artery was patent and functioning well. Vein bypass grafts to the circumflex system and to the right coronary artery were also patent. In both cases, ventriculography demonstrated improved motion of the hypokinetic anterior wall segments. The remaining four patients are asymptomatic but have been reluctant to undergo postoperative catheterization studies.

Discussion

Several studies have utilized pre- and postoperative electrocardiograms and vectorcardiograms to assess the incidence of myocardial infarction after coronary arterial bypass surgery. QRS changes of transmural myocardial infarction have been reported in 8 to 30 percent of patients having such surgery.[1,2,8–10] Despite the development of new Q waves many of these patients have an uncomplicated postoperative course[8,11] and many have unchanged or even improved left ventricular contraction on postoperative angiography.[11] Bassan et al.[11] suggested that in some patients after coronary arterial surgery new Q waves developed in the inferior leads as the result of relief of the anteroapical ischemia that had been canceling[12] the loss of opposing forces of an old infarcted area in the posteroinferior wall. They[11] also presented two cases of enhanced R waves in the precordial leads in electrocardiograms after bypass to the left anterior descending coronary artery. Our report describes six patients whose electrocardiographic patterns of anterior wall myocardial infarction were abolished after coronary bypass surgery and whose vectorcardiograms corroborated the loss of the infarction patterns and the return of normal anterior QRS forces postoperatively. The pre- and postoperative vectorcardiograms in our six cases clearly exclude the possibility that differences in lead placement or a canceling effect[12] of a new posterior wall infarction caused the electrocardiographic changes. Our observations suggest that the preoperative electrocardiographic and vectorcardiographic patterns of infarction were secondary to myocardial ischemia rather than an indication of frank infarction and that with revascularization surgery and improved perfu-

sion to ischemic areas anterior QRS forces returned to normal.

Myocardial ischemia and reversible electrical patterns of infarction: Earlier experimental and clinical reports[13–18] have shown that myocardial ischemia can produce electrically silent areas and reversible electrocardiographic patterns of myocardial infarction. Gross et al.[13] produced experimental myocardial ischemia in dogs by ligating either the circumflex or anterior descending coronary artery. In one third of their animals, typical Q waves appeared that disappeared within 3 to 5 minutes after removal of the ligature; subsequent pathologic studies failed to demonstrate significant myocardial necrosis. They concluded that the transitory Q waves represented a reversible stage of metabolic aberration of the myocardium during acute ischemia. Clinically, transient Q waves have been documented during coronary insufficiency[15] and attacks of angina pectoris[16] and during or after supraventricular or ventricular tachycardia.[17] Haiat and Chiche[4] have suggested that electrocardiographic patterns of myocardial infarction may disappear when there is recovery of superficial layers of ischemic myocardium surrounding an old infarcted area and that old patterns of infarction may reappear with subsequent ischemia to surrounding superficial layers of myocardium. Klein et al.[18] described transient electrocardiographic patterns of myocardial infarction including abnormal Q waves during open heart surgery. They attributed these transient patterns to reversible myocardial ischemia as the result of cross-clamping of the aorta, cardiopulmonary bypass, perfusion of the coronary arteries with cooled blood and localized abnormalities of membrane potentials and electrolytes. Their observations as well as our findings strengthen the concept that electrically inert areas of myocardium may be altered and do not always imply myocardial cell death. It appears that myocardial ischemia in certain instances can produce electrical patterns of infarction that may be reversible upon reestablishment of perfusion to ischemic areas.

Role of fascicular conduction defects: Left anterior fascicular block may be associated with diminutive anterior QRS forces and Q waves in the right precordial leads in scalar electrocardiograms in the absence of anterior myocardial infarction.[19,20] Theoretically, improved anterior fascicular conduction might lead to an augmentation of anterior QRS forces. Patient 2 (Fig. 1 and 2) had left anterior hemiblock preoperatively; postoperatively, left axis deviation was less marked although still present, and anterior QRS forces were dramatically increased. Since left axis deviation persisted in the postoperative frontal plane vectorcardiogram, improved anterior fascicular conduction is not a likely explanation for the generous augmentation of anterior QRS forces. The development of left posterior fascicular block in patients with anterolateral infarction may, in certain instances, cause disappearance of Q waves in the precordial leads of standard electrocardiograms.[21] In our six patients, postoperative vectorcardiograms did not show significant right axis shift in the frontal plane to implicate posterior fascicular damage. Hence, fascicular block contralateral to the infarcted area could not explain the disappearance of precordial lead Q waves in the scalar electrocardiograms or the appearance of more normal anterior QRS forces in the postoperative vectorcardiograms.

Focal intraventricular block involving septal forces: Abnormal slowing of initial QRS forces was noted in the preoperative vectorcardiograms of our patients. In all cases slow initial activation persisted in the postoperative vectorcardiograms in association with augmentation of anterior forces. One might conclude that the abnormal initial forces are the result of an intraventricular conduction disturbance and that postoperatively different electrical pathways are utilized. Gambetta and Childers[19] described two patients with coronary artery disease who had rate-dependent pathologic Q waves in leads V_1 to V_3 of scalar electrocardiograms. They suggested that these patients had a focal block in septal fibers of the left bundle branch system and that such a defect could underlie the development of transient right precordial lead Q waves seen in myocardial ischemia without frank infarction. There is now evidence to support the existence of such septal ramifications of the left bundle and, theoretically, block could take place at this level.[22] One might postulate that ischemia secondary to coronary arterial stenosis produced block in fibers responsible for normal septal activation and that successful revascularization allowed more normal or alternate conduction patterns to ensue. Whether abnormal initial QRS patterns simulating myocardial infarction and secondary to ischemia are the result of block in normal septal pathways or block at the level of the myocardium, these patterns are potentially reversible and do not always imply necrosis of heart muscle.

Electrical patterns of infarction and ventricular asynergy: In selecting patients for coronary arterial bypass surgery, it may be difficult to determine whether or not abnormalities of myocardial contraction on ventriculography are secondary to myocardial fibrosis or myocardial ischemia. Jacob et al.[23] recently attempted to utilize preoperative electrocardiograms and vectorcardiograms to predict the effect of coronary bypass surgery on localized areas of ventricular asynergy. They found that hypokinetic segments on ventriculography associated with electrocardiographic or vectorcardiographic patterns of infarction were less likely to improve after coronary bypass surgery than hypokinetic segments not associated with such patterns of infarction. Although our study reflects only a small percent of patients undergoing coronary arterial surgery, our observations indicate that preoperative electrocardiographic and vectorcardiographic patterns of infarction do not always imply irreversible myocardial damage. For example, before operation two of our patients had both a QRS pattern of anterior wall infarction in electrocardiograms

and vectorcardiograms and a normal pattern of anterior wall contraction in ventriculograms. Two additional patients who underwent postoperative cardiac catheterization studies manifested improved motion of hypokinetic anterior wall segments in ventriculograms as well as regeneration of anterior QRS forces in electrocardiograms and vectorcardiograms.

Clinical implications: The reappearance of anterior QRS forces in both the electrocardiograms and vectorcardiograms of six patients after coronary revascularization surgery supports previous clinical observations and experimental data suggesting that electrically silent areas of myocardium are not always synonymous with myocardial cell death. In certain patients, chronic myocardial ischemia may produce electrocardiographic and vectorcardiographic patterns indistinguishable from those of anterior wall myocardial infarction. In view of modern surgical techniques that, in selected cases, allow for successful myocardial revasulcarization, it is important to distinguish between myocardium that is chronically ischemic and that which is fibrotic and irreversibly damaged. The commonly held belief that Q waves in standard electrocardiograms can be equated with myocardial fibrosis and irreversible scarring is not always valid. Such electrocardiographic changes must be cautiously weighed along with other objective data in the evaluation of patients who are symptomatic with angina pectoris.

Acknowledgment

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Significant Sex Differences in the Correlation of Electrocardiographic Exercise Testing and Coronary Arteriograms

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Two hundred fifty-one patients (195 male and 56 female) referred for evaluation of chest pain were studied by multistage submaximal stress testing and selective coronary arteriography. In men with positive exercise tests the incidence rate of true positive exercise test results—that is, positive tests associated with 75 percent or greater coronary stenosis—was 89 percent in contrast to a 33 percent incidence rate of true positive exercise test results in women. The incidence rate of false positive excercise test results—that is, positive tests associated with no coronary stenosis or less than 50 percent stenosis—was 8 percent in men in contrast to 67 percent in women. Conversely, the incidence rate of false negative exercise test results (that is, negative exercise tests associated with 75 percent or greater coronary stenosis) was higher in men (37 percent) than in women (12 percent). It is concluded that in men a positive multistage stress test is useful in predicting the presence of significant coronary artery disease although a negative stress test cannot be relied upon to rule out the presence of significant disease. In women, a positive exercise test is of little value in predicting the presence of significant coronary artery disease, whereas a negative test is quite useful in ruling out the presence of significant disease. New criteria should be developed for stress testing of women.

The accuracy of different methods of stress testing in predicting the presence or absence of significant coronary artery disease has been variously reported.[1–8] Differences in the reported incidence of true positive and false positive exercise test results may be due to the type of exercise performed, the electrocardiographic leads recorded after exercise, the criteria by which an exercise test is interpreted as "positive" or "negative," or judged to be truly positive or falsely positive, and other factors such as drugs, electrolyte imbalance or associated disease. The studies of Lepeschkin[9] and Astrand[10,11] as well as the reviews by Bruce[12] and Blomqvist[5] suggest an important difference between men and women in their response to exercise. To our knowledge the influence of sex on the correlation between submaximal stress tests and selective coronary arteriographic results has not been reported.

This retrospective study describes our experience in correlating 12 lead electrocardiographic submaximal stress test results with the results of selective coronary arteriographic studies specifically evaluating the influence of sex upon this correlation.

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TABLE I

Method of Scoring Severity of Coronary Disease

Single Lesion		Multiple Lesions	
Degree of Narrowing (%)	Index Score	Most Severe Degree of Narrowing (%)	Index Score
50–74	1	50–74	2
75–94	2	75–94	3
95–99	4	95–99	4
100	4	100	4

Each major coronary vessel received an index score according to this table. The sum of scores from all vessels represented the "severity index."

TABLE II

Distribution of Results of Exercise Tests and Coronary Arteriograms

Subjects	Total		Men		Women	
	no.	%	no.	%	no.	%
Total group	251	100	195	78	56	22
With positive exercise test (≥1 mm S-T depression)	77	31	62	32	15	27
With significant coronary artery disease (≥75 percent narrowing)	114	45	104	53	10	18
With narrowing of one or more vessels (≥50 percent)	122	49	111	57	11	20

Methods and Material

Patients: Two hundred fifty-one subjects referred for evaluation of chest pain were studied. There were 195 men (78 percent) and 56 women (22 percent). The mean age of the male subjects was 48.4 years (±9.2 standard deviation) and of the female subjects, 50.0 years (±8.4). Patients suffering from valvular heart disease, myocarditis or pericarditis, primary myocardial disease, anemia, thyroid disease or electrolyte imbalance were excluded. No patient was receiving digitalis, propranolol or quinidine sulfate during the 2 weeks preceding exercise testing.

Exercise testing: All patients performed graded treadmill stress testing according to the method of Bruce and Hornsten.[13] Exercise was discontinued when the patient attained a heart rate of 85 percent of maximal predicted for age,[14] complained of significant chest pain, shortness of breath, dizziness or lightheadedness or had S-T segment depression in excess of 3 mm. The mean postexercise heart rate in men was 141 beats/min (±19) and in women, 146 beats/min (±17). Standard 12 lead electrocardiograms were recorded at rest before exercise, immediately after exercise (within 30 seconds) and 2 and 6 minutes after exercise. Subsequent electrocardiograms were obtained if the 6 minute postexercise tracing revealed that the S-T segments had not returned to the preexercise configuration. The electrocardiograms were recorded with a Sieman Mingograph 6t recorder with patients in the supine position.

Postexercise electrocardiograms were classified as showing: (1) no S-T segment depression, (2) 0.5 to 0.9 mm S-T segment depression, (3) 1 to 1.9 mm S-T segment depression, (4) 2 to 2.9 mm S-T segment depression, or (5) 3 mm S-T segment depression. Only those postexercise electrocardiograms with 1 mm or greater S-T segment depression of at least 0.8 second's duration were considered positive tests. An additional requirement for a positive test was that the S-T segments be flat or downward sloping. If the resting electrocardiogram manifested nonspecific S-T segment depression at rest, a flat or downward sloping depression of 0.8 second's duration and at least 1 mm greater than that present at rest was also considered to represent a positive test. These changes could be present in any lead and at any time interval after exercise. Negative test results were recorded when the S-T segment depression was 0.9 mm or less.

Coronary arteriography: Selective coronary arteriographic studies were performed in all patients by the method of Sones and Shirey,[15] using a solution of 29.1 percent sodium diatrizoate and 28.5 percent meglumine diatrizoate containing 31 percent iodine (Renovist II®, E. R. Squibb and Sons) as the opacifying medium. Opacification was visualized with a General Electric 6 and 9 inch image intensifier, the output of which was recorded in both modes on 35 mm film at a rate of 60 frames/sec and on 105 mm film at a rate of 2 frames/sec. Multiple views of the coronary arteries in both the right and left anterior oblique projections were obtained in each case. All lesions were classified as single or multiple, and the severity of the lesions classified as narrowing of a vessel's diameter by less than 50 percent, 50 to 74 percent, 75 to 94 percent, more than 95 percent or total occlusion. A coronary arteriogram was considered positive and to indicate significant coronary artery disease if one or more major vessels manifested a stenotic lesion equal to or greater than 75 percent of its diameter in any projection. Patients with no angiographically visualized lesion or with stenosis of 49 percent or less of a vessel's diameter were considered, for the purpose of this study, to have normal coronary arteriograms or insignificant coronary artery disease. The severity of occlusive coronary artery disease was determined by calculating the "severity index" as outlined in Table I.

Results

Thirty-two percent of male subjects (62 of 195) and 27 percent of female subjects (15 of 56) had positive exercise tests. In contrast, 53 percent of men (104 of 195) as compared with only 18 percent of women (10 of 56) had positive coronary arteriograms manifesting significant coronary artery disease (that is, 75 percent or greater narrowing) (Table II).

False positive results: The correlation between exercise test results and arteriographically visualized coronary occlusive lesions is depicted in Table III. Overall, 78 percent (60 of 77) of the subjects (male and female) with positive exercise tests had angiographically demonstrated significant coronary occlusive lesions (75 percent or greater narrowing). This positive relation is due primarily to the high rate of correlation in men. In men, the incidence rate of true positive exercise test results was 89 percent (55 of 62), whereas in women it was only 33 percent (5 of 15). This difference is highly significant statistically

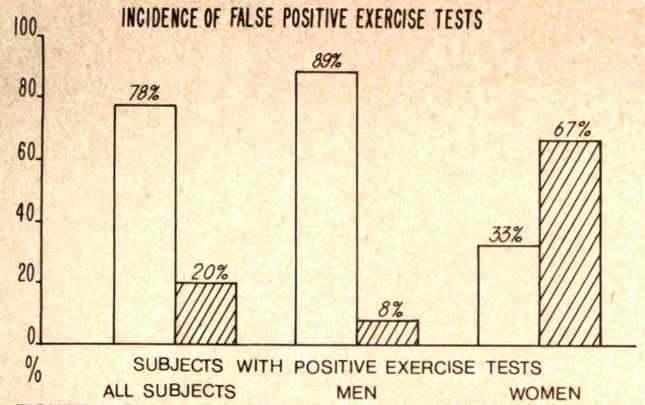

FIGURE 1. The marked difference in the incidence of false positive exercise tests between men and women is statistically significant (Table III). **Hatched bars** indicate percent of positive exercise tests associated with normal coronary arteries or less than 50 percent stenosis (false positive tests). **Open bars** indicate percent of positive tests associated with 75 percent or greater coronary stenosis.

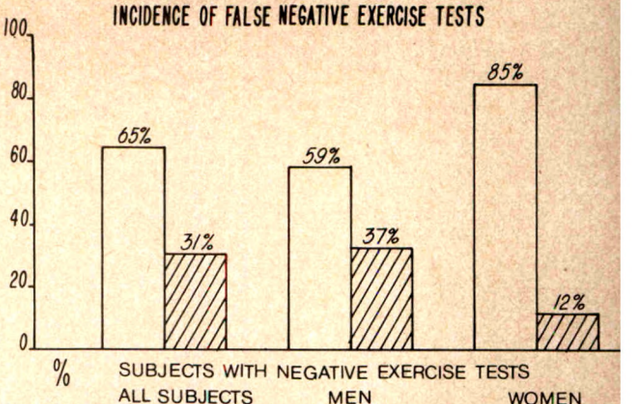

FIGURE 2. The difference in the incidence of false negative exercise tests between men and women is statistically significant (Table III). **Hatched bars** indicate percent of negative exercise tests associated with 75 percent or greater coronary stenosis (false negative). **Open bars** indicate percent of negative tests associated with normal coronary arteries or less than 50 percent stenosis.

(P <0.001). If one accepts 50 percent or greater narrowing as a significant lesion the relation remains essentially unchanged (Table III). From these incidence rates of true positive exercise tests, it follows that the overall incidence rate of false positive exercise tests is 22 percent, with an 11 percent incidence rate in men and a 67 percent incidence rate in women. This assumes, however, that all lesions in which a vessel was narrowed by less than 75 percent of its diameter were insignificant. If one accepts only lesions of less than 50 percent narrowing as insignificant the overall incidence rate of false positive exercise test results is 20 percent (15 of 77), with an 8 percent rate (5 of 62) in men and a 67 percent rate (10 of 15) in women. In both instances, the difference between sexes is again highly significant statistically (P <0.001) (Table III, Fig. 1).

False negative results: Overall, 31 percent (54 of 174) of the subjects (male and female) with negative exercise tests had angiographically demonstrated significant coronary occlusive lesions (75 percent or greater narrowing). In contrast to false positive exercise test results, the false negative exercise tests occurred primarily in male subjects. The incidence rate of false negative exercise test results was 37 percent (49 of 133) in men but only 12 percent (5 of 41) in women. Again the difference in incidence between sexes is statistically significant (P <0.01) (Table III, Fig. 2). These results are not significantly altered if one accepts 50 percent stenosis of a vessel as significant disease (Table III).

There was no significant difference in either the number of vessels involved or the severity of disease between men and women who were demonstrated to have either false positive or false negative exercise test results (Tables I and IV).

Electrocardiographic leads involved: The leads in which significant S-T segment depression (1 mm or more) occurred are depicted in Table V. In all

TABLE III

Correlation of Results of Exercise Tests and Coronary Arteriograms in Men and Women

Subjects	Men no.	Men %	Women no.	Women %	P
Positive exercise test					
With ⩾75 percent narrowing of one or more vessels	55	89*	5	33*	<0.001
With ⩾ 50 percent narrowing of one or more vessels	57	92*	5	33*	<0.001
With normal coronary arteries or <75 percent narrowing	7	11*	10	67*	<0.001
With normal coronary arteries or <50 percent narrowing	5	8†	10	67†	<0.001
Negative exercise test					
With >75 percent narrowing of one or more vessels	49	37†	5	12†	<0.01
With >50 percent narrowing of one or more vessels	54	41†	6	15†	<0.01

*Percent of sex with positive exercise tests (Table II).
†Percent of sex with negative exercise tests (Table II).
P = probability.

subjects lead V_5 most consistently manifested the significant S-T segment depression (92 percent of subjects; 69 of 75). If the depression was not manifested in this lead it was seen in each of leads II, III and aVF (two women and three men) with one exception, a man whose S-T segment depression was seen in lead V_4 alone. Among subjects with positive exercise tests, significant S-T segment depression in lead II occurred in 73 percent of women compared with 25

TABLE IV

Number of Vessels Narrowed and Index of Severity of Disease (mean no. ± standard deviation)

	Men			Women		
	no. of Vessels Narrowed			no. of Vessels Narrowed		
	⩾50%	⩾75%	Severity Index*	⩾50%	⩾75%	Severity Index*
Subjects with positive exercise test and one or more vessels narrowed ⩾75%	2.1 ± 0.8	1.8 ± 0.8	6.5 ± 2.5	2.0 ± 0.6	2.0 ± 0.6	6.6 ± 2.1
Subjects with negative exercise test and one or more vessels narrowed ⩾75%	1.9 ± 0.8	1.7 ± 0.7	5.3 ± 2.6	1.4 ± 0.8	1.4 ± 0.8	5.0 ± 3.1

* The mean numbers represent the mean severity index derived from the sum of all severity indexes determined for each subject in the group according to Table I.

TABLE V

Electrocardiographic Leads in Which Postexercise S-T Segment Depression Occurred

	Sex	Total no. of Subjects	Electrocardiographic Leads											
			I	II	III	aVR	aVL	aVF	V_1	V_2	V_3	V_4	V_5	V_6
True positive exercise tests (positive exercise tests correctly predicting the presence of significant coronary artery disease (⩾75% narrowing)	M	55	7	14	9	...	1	12	1	13	23	45	52	51
	F	5	...	2	2	...	...	2	...	...	2	3	3	2
False positive exercise tests (positive exercise test associated with either no occlusive coronary artery disease or narrowing <50%)	M	5	...	1	1	...	...	1	...	...	1	3	5	5
	F	10	3	9	5	...	...	8	...	...	1	5	9	9

TABLE VI

Relation of Coronary Arteriographic Findings to Postexercise S-T Segment Depression

Coronary Arteriographic Findings	Degree of S-T Segment Depression					
	1–1.9 mm		2–2.9 mm		>3 mm	
	Men	Women	Men	Women	Men	Women
One or more vessels with ⩾50% narrowing	25	4	18	0	14	1
One or more vessels with ⩾75% narrowing	23	4	18	0	14	1
No narrowing or <50% narrowing	3	9	1	1	1	0

percent of men. This difference is statistically significant at the 95 percent confidence level. Further, 90 percent of women with false positive exercise tests had significant S-T segment depression in lead II in contrast to 40 percent of women with true positive exercise tests. This apparently useful point of differentiation is derived from a small population and is not statistically significant.

Comments

Exercise testing has proved to be one of the most useful noninvasive methods of evaluating ischemic heart disease. Unfortunately, discrepancy exists in reports that have evaluated the accuracy with which the results predict the presence of significant coronary artery disease.[1–7] To our knowledge, although the Master exercise test differentiates between male and female subjects,[16] there have been no reports as to the significance of sex in the interpretation of submaximal stress tests. Nevertheless, previously cited reports[5,9–12] suggest an important difference in the physiologic response of men and women to exercise.

Our study strongly supports the contention that there is a significant difference in the results obtained in the exercise testing of men and women. This difference may, at least in part, explain the discrepancies in the reported incidence of true and false positive exercise test results.

In our study, significant coronary artery disease was correctly predicted by exercise testing in 78 percent of all patients, both male and female, a statistic not differing greatly from data in other reported series.[3,6,7] However, separate analysis of our data indicates that the ability of an exercise test to predict correctly the presence of significant coronary artery disease is appreciably better in men (89 percent true positives) than in women (33 percent true positives). The overall incidence rate of false positive exercise test results in our series was 20 percent, which again is not very different from that of other reported series. It is extremely important to note, however, that the incidence rate in men was only 8 percent as compared with 67 percent in women. Further, our study reveals an overall occurrence of false negative exercise tests of 31 percent, but, in contrast to false positive exercise test results, the incidence was appreciably higher in men (37 percent) than in women (12 percent).

Neither the severity of disease nor the number of vessels significantly occluded correlated with these differences between the sexes. Although significant S-T segment depression occurred more frequently in leads II, III and aVF in women than in men, its presence in these leads did not aid in differentiating true and false positive exercise tests.

Although false positive exercise test results were rarely seen in the presence of greater than 2 mm of postexercise S-T segment depression, a depression in excess of 2 mm or even 3 mm is not an absolute predictor of the presence of significant coronary artery disease (Table VI).

Clinical implication: We conclude that, in men, a positive multistage exercise test is useful in predicting the presence of significant coronary artery disease; but a negative test cannot be relied upon to rule out such disease. In women, a positive exercise test is of little value in predicting the presence of significant coronary artery disease although a negative test is useful in ruling out its presence. We believe that new criteria should be developed for exercise testing of women and are investigating this possibility.

Cause of false positive tests in women: The explanation for this high and unacceptable incidence rate of false positive exercise test results in women is unclear. However, Bruce[12] has pointed out that postexertional S-T segment depression in middle-aged women may partly be due to lower levels of hematocrit and total circulating red cell mass. Further, recent unpublished observations by Kusumi and Bruce[12] have revealed "higher pulmonary and systemic resistances with higher pressure-rate products in asymptomatic middle-aged women who exhibit S-T depression after maximal exercise."

The use of digitalis glycosides is known to be associated with an increased incidence of false positive exercise test results.[17] Digitalis and estrogen have a similar chemical structure. One of the side effects of digitalis mimics an estrogen effect, that is, gynecomastia. Theoretically, therefore, it is conceivable that estrogens may at least be partially responsible for the high incidence rate of false positive exercise test results in women.

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Addendum

A recent article (Cumming GR, Dufresne C, Kich L, et al: Exercise electrocardiogram patterns in normal women. Br Heart J 35:1055–1061, 1973) also noted a very high incidence rate of false positive exercise test results in women and stated that "exercise electrocardiography is of limited value in women."

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Comparison of Angiographic and Postmortem Findings in Patients with Coronary Artery Disease

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The accuracy of coronary cineangiography in predicting the degree of stenosis in coronary arteries was evaluated by comparing autopsy and premortem cineangiographic findings in 25 patients. Coronary cineangiograms and autopsy specimens were reviewed independently by two cardiologists and two pathologists. Identical diagrams dividing the coronary arteries into 12 segments were used by both groups to record the location and degree of stenosis observed. Cineangiographic findings were in agreement with pathologic findings (less than 25 percent difference in cross-sectional luminal area) in 178 (79 percent) of the 226 segments examined, but overestimated the degree of stenosis in 13 (6 percent) and underestimated it in 34 (15 percent). Thus, cineangiography appears to be a reliable tool in evaluating coronary artery disease. When diagnostic errors are made, they are usually underestimations of the degree of disease; common causes of error are circumferential stenosis, eccentric lesions, obstruction of view by artificial valves and poor opacification due to severe proximal stenosis.

Successful application of surgical treatment of coronary artery disease greatly depends on accurate determination of the severity and location of the occlusive lesions in the coronary arterial system. The accuracy of coronary cineangiography is of critical importance not only in the diagnosis but also in the proper management of patients with coronary artery disease.

Angiography is generally accepted as a reliable tool in estimating the degree and extent of arterial disease although there are only a few studies correlating angiographic with anatomic findings.[1–6] These reports generally agree that when angiographic errors occur, they are usually underestimations of the stenotic lesions. However, there is no agreement on either the reliability of the technique or the cause of major errors.

This study of 25 patients was undertaken to compare premortem angiographic data with data on postmortem anatomic specimens of the coronary arteries. The reliability and accuracy of angiography, reasons for error and problems encountered due to poor visualization of vessels are analyzed.

Methods

Twenty-five patients who died after either aortocoronary bypass or valvular surgery, or both, between October 1968 and January 1973 were included in the study. All patients had selective coronary cineangiograms before surgery and only one did not have severe coronary artery disease. The interval between angiography and postmortem examination was less than 1 month in 16 cases, 1 to 4 months in 7 and greater than 4 months in 2 cases (the longest interval was 10 months).

Selective coronary cineangiograms in multiple projections were obtained with use of the Judkins transfemoral technique[7] and filmed at 60 frames/sec

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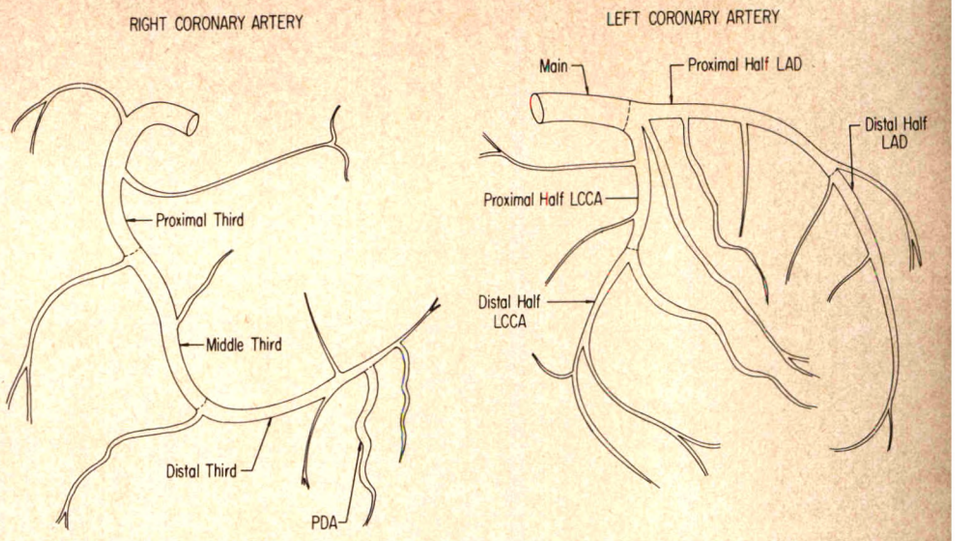

FIGURE 1. Diagram used to record lesions found in the coronary arteries by both anatomic dissection and cineangiography. LAD = left anterior descending artery; LCCA = left circumflex artery; PDA = posterior descending artery.

on 35 mm Kodak double X film. A Phillips cinefluorographic unit with a 5 inch image intensifier was used in eight cases and a Picker biplane unit with 9 inch image tubes and overframing lens was employed in nine; the remaining eight cases were studied with a Picker biplane Pulsar cinefluorographic unit with 6 inch image tubes and additional photographic magnification with zoom lenses. Since the result was not significantly different with respect to the cinefluorographic unit used, the data of all patients were analyzed as one group.

All cine films were reviewed independently by two angiographers without prior knowledge of the anatomic findings. The severity and location of all stenotic lesions were recorded on the diagrams shown in Figure 1. The degree of stenosis was estimated in percent decrease in luminal diameter. From these data, the percent decrease in cross-sectional area was then calculated for comparison with pathologic findings.

At the time of postmortem examination, the heart was removed in toto, photographed and weighed, and X-ray films were taken. Polyethylene catheters were then inserted into the coronary arterial orifices and tied into place. After flushing with normal saline solution, a fine colloidal suspension of barium (micro-opaque) was injected at 100 mm Hg of pressure over a 20 minute period. After fixation in 20 percent phosphate-buffered 0.02 molar formalin, radiographs of the heart were again obtained. If the coronary arteries were not calcified, they were examined in 2 to 3 mm serial sections. If calcium was present, the arteries were dissected free of the heart in toto and decalcified; X-ray films were taken and 2 to 3 mm serial sections examined. The specimens were reviewed by two pathologists, and the location and severity of stenosis in terms of percent decrease in cross-sectional area were recorded on diagrams identical to those used by the cardiologists.

The angiographic and pathologic findings were then compared using the latter as the standard of accuracy. Whenever, for technical reasons, an accurate evaluation of a segment could not be made from either the angiogram or the pathologic specimen, that segment was not included in the comparison. For example, segments were excluded for the following reasons: (1) inadequate opacification during premortem angiography, (2) surgical removal of lesions by endarterectomy, (3) distortion of the ostium as a result of postmortem insertion of a cannula, and (4) inadequate postmortem decalcification resulting in distortion of the lumen.

Correlation between the studies was recorded as follows: Complete agreement was designated if the anatomic and angiographic estimations of luminal area were within 25 percent of each other. When the in vivo angiographic estimation of luminal area was less than that found postmortem, the underestimation was quantified as −1 when the difference was 25 to 49 percent, −2 when it was 50 to 74 percent and −3 when it was 75 percent or more. When angiography overestimated the degree of stenosis, overestimations were similarly graded from +1 to +3.

Results

Table I shows the segments examined, the frequency of agreement between the findings and the degree of error when disagreement occurred. In both the right and left coronary arteries the correlation between angiographic and anatomic findings was significantly greater in the proximal than in the distal segments ($P < 0.05$). Among 226 segments studied the findings were in agreement in 179 (79 percent); overestimations occurred in 13 (6 percent) and underestimations in 34 (15 percent). Thirteen of the latter (6 percent) were underestimations of 75 percent or greater.

Since 75 percent stenosis of a vessel is generally accepted as the point where blood flow is significantly decreased,[8] we examined the reliability of angiographic estimates in relation only to vessels with 75 percent or greater narrowing (Table II). No statistically significant difference was found in the accuracy of angiographic estimates between proximal and distal segments, perhaps because of the small number of these segments with severe lesions. However, the disagreements that did occur in this group were almost always underestimations of 75 percent or greater.

There were 17 segments that could not be visualized by cineangiography but were examined anatomi-

TABLE I

Correlation of Data on All Segments Examined

Coronary Arterial Segments	Comparisons (no.)	Complete Agreement	Disagreement*				
			−1	−2	−3	+1	+2
RCA							
Ostium	11	10 (91%)	0	1	0	0	0
Prox 1/3	24	20 (83%)	0	0	2	1	1
Mid 1/3	21	18 (86%)	0	0	2	1	0
Dist 1/3	19	13 (68%)	1	2	1	1	1
PDA	16	12 (75%)	1	2	1	0	0
LCA							
Ostium	14	12 (86%)	1	0	1	0	0
Main	24	17 (71%)	3	4	0	0	0
LAD, prox 1/2	24	23 (96%)	0	0	1	0	0
LAD, dist 1/2	20	15 (75%)	0	1	2	1	1
Diagonal	8	5 (63%)	0	1	1	1	0
LC prox	24	19 (79%)	0	2	2	0	1
LC dist	21	15 (71%)	1	1	0	3	1
Total	226	179 (79%)	7 (3%)	14 (6%)	13 (6%)	8 (4%)	5 (2%)

*−1, −2 and −3 indicate angiographic underestimations of 25 to 49, 50 to 74, 75 or greater percent, respectively. +1 and +2 indicate angiographic overestimations of 25 to 49 and 50 to 74 percent, respectively.

Dist = distal; LAD = anterior descending branch of left coronary artery; LCA = left coronary artery; LC = left circumflex artery; Mid = middle; PDA = posterior descending artery; Prox = proximal; RCA = right coronary artery.

cally (Table III). Except for the diagonal branch, all segments not visualized were in more distal parts of the vessel, and all 17 segments were distal to a stenosis of 75 percent or greater in the more proximal segment. Within the nonvisualized segments stenotic lesions of 75 percent or greater were found in 10 (59 percent), and stenosis of 50 to 74 percent was found in 6 (35 percent).

Reasons for major errors: The 13 segments in which underestimations of 75 percent or more occurred were examined to determine the reason for these major errors. Figure 2 illustrates some of the sources of error that were found. Vessels with elongated circumferential lesions were often interpreted as "small but otherwise normal" on the basis of angiograms, but anatomically some of these vessels were 90 percent occluded; two of the 75 percent underestimations were made because of this type of lesion. Eccentric, slitlike or "fish mouth" lesions were implicated in four underestimations. In two hearts prosthetic valves were the cause of major errors due to obstruction of view. The probable cause of some misinterpretations was a severe proximal lesion. If a proximal vessel was obstructed by a lesion of only 25 percent or less, there was 82 percent agreement in the findings in the distal vessels. However, when there was a stenotic lesion of 75 percent or more in the proximal vessel, the accuracy of angiographic interpretation of distal vessels decreased to 63 percent.

Discussion

This study demonstrates that cineangiography is a reliable tool in the evaluation of coronary artery disease. However, occasional major errors do occur, usually underestimations of the obstruction of the luminal area, predominantly in vessels that have severe disease. There is also a greater incidence of error in distal segments, which may be due to the smaller caliber of vessels distally and to the streaming of contrast medium and inadequate opacification distal to lesions in the proximal segments.

Although the exact reasons for some of the misinterpretation could not be determined, the cause of error was found in many cases. Circumferential lesions with a central lumen involving a long segment were a frequent source of error. This problem occurred because angiography visualizes the vessel lumen but not the vessel wall, and the luminal size in areas adjacent to the lesion is frequently used as normal reference in determining luminal diameter. When the entire artery, or even many vessels in the same heart, is diseased, these comparisons can be misleading because of the lack of a true normal frame of reference. Eccentric or "fish mouth" lesions also accounted for a few errors. When viewed from one angle, the eccentric lesions may appear normal and thus lead to serious error. Artificial valves in this series were related to two errors caused by obstruction of view. The last major reason for error was the presence of severe proximal lesions because contrast medium does not always fill the distal segment adequately for proper evaluation. One must be cautious, therefore, when interpreting luminal patency distal to a severe proximal lesion. This is particularly important when aortocoronary bypass surgery is contemplated. In this regard, it is also important to note that 17 segments that could not be visualized on angiography had significant disease throughout their

TABLE II

Correlation of Data on Only Those Segments with 75 Percent or Greater Anatomic Lesions

Coronary Arterial Segments	Comparisons (no.)	Complete Agreement	Disagreement				
			−1	−2	−3	+1	+2
RCA							
Ostium	1	1 (100%)	0	0	0	0	0
Prox 1/3	15	13 (87%)	0	0	2	0	0
Mid 1/3	14	12 (86%)	0	0	2	0	0
Dist 1/3	9	8 (89%)	0	0	1	0	0
PDA	5	3 (60%)	0	1	1	0	0
LCA							
Ostium	1	0 (0%)	0	0	1	0	0
Main	6	5 (83%)	0	1	0	0	0
LAD, prox 1/2	22	21 (95%)	0	0	1	0	0
LAD, dist 1/2	6	4 (67%)	0	0	2	0	0
Diagonal	5	4 (80%)	0	0	1	0	0
LC prox	16	14 (88%)	0	0	2	0	0
LC dist	3	3 (100%)	0	0	0	0	0
Total	103	88 (85%)	0	2 (2%)	13 (13%)	0	0

Abbreviations and symbols as in Table I.

TABLE III

Coronary Segments Not Visualized

Coronary Arterial Segments	no.	Anatomic Lesions*			
		0–24%	25–49%	50–74%	≥75%
RCA					
Ostium	0	0	0	0	0
Prox 1/3	0	0	0	0	0
Mid 1/3	3	0	0	2	1
Dist 1/3	5	1	0	1	3
PDA	5	0	0	2	3
LCA					
Ostium	0	0	0	0	0
Main	0	0	0	0	0
LAD, prox 1/2	0	0	0	0	0
LAD, dist 1/2	2	0	0	0	2
Diagonal	1	0	0	1	0
LC prox	0	0	0	0	0
LC dist	1	0	0	0	1
Total	17	1 (5.8%)	0 (0%)	6 (35.4%)	10 (58.8%)

* Occlusive lesions in vessels.
Abbreviations as in Table I.

entire length and were not suitable for bypass grafting.

Review of previous correlative studies: Although there are several reported studies correlating the angiographic and anatomic findings in patients with coronary artery disease, many include only a small number of patients, compare only the postmortem angiogram with the anatomic findings, or include patients with a prolonged time interval between angiography and death. In 1962, Grey et al.[1] compared postmortem coronary angiograms with anatomic findings in 13 patients. Among 93 segments that appeared normal or minimally diseased (questionable narrowing) in postmortem angiograms, 39 (42 percent) were found to have more severe disease on postmortem dissection. Eusterman et al.[2] carried out a similar study in 50 postmortem hearts. With focal stenosis, there was an excellent correlation between the angiographic and the anatomic findings. However, in arteries with diffuse disease, they found that the angiographic data underestimated the severity of disease in 86 percent of the segments and overestimated it in 3 percent. In 1963, Hale et al.[3] concluded from a study of four patients that "the worst possible assessment of a lesion demonstrated in life is probably the more accurate." Kemp et al.[4] in 1967 evaluated the accuracy of 29 premortem angiograms with postmortem anatomic data. They divided arteries into five segments, and found only three errors of functional significance. The quality of the arteriogram was judged the most important factor in accurate evaluation. Vlodaver et al.[5] studied 10 cases, comparing premortem angiograms with postmortem examination of the anatomic lesions. They called an

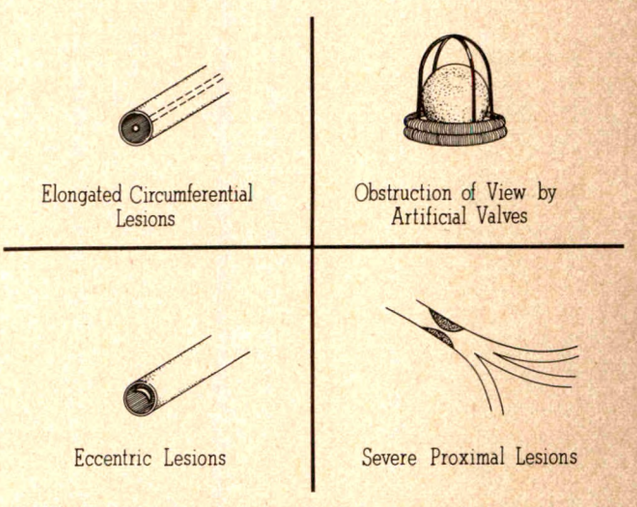

FIGURE 2. Pictorial representation of causes of cineangiographic underestimations with 75 percent or more stenosis.

error false negative if the coronary arteriogram showed less than 50 percent obstruction of luminal diameter when the anatomic lesion was actually more than 50 percent obstructed. An error was called false positive if the reverse was true. They divided vessels into six segments. Of a total of 134 segments examined, data were in agreement in 86 (64 percent); there were 44 (33 percent) false negatives and 5 (4 percent) false positives. In their study the intermediate segment of the right coronary artery (our middle third), the main left coronary artery and the proximal half of the circumflex artery were all particularly prone to underestimation. Slitlike or eccentric lesions were also common sources of error.

Grondin et al.[6] studied 28 patients who died after saphenous vein bypass grafting. In only 23 of these cases were both the preoperative angiograms and postmortem specimens suitable for comparison. They found nine instances of major disagreement between the two techniques. A variety of explanations were given, including circumferential lesions, overlapping of vessels, diffuse disease and short takeoffs of vessels.

Our data agree with previous findings that coronary cineangiography is an accurate tool in defining coronary anatomy. When error occurs, angiography frequently underestimates the lesion. In addition, accuracy is reduced in more distal parts of the arterial tree, especially in the presence of severe stenosis in the proximal segment. When a segment cannot be opacified either by antegrade or retrograde filling, it is usually found to be severely diseased on postmortem dissection.

Clinical implications: To improve the accuracy of coronary cineangiography, it is imperative to opacify the coronary arteries selectively and in appropriate projections to assure that all segments of the arterial tree are adequately visualized in a plane perpendicular to the X-ray beam. In addition to the multiple still projections, we have found that cineangiograms obtained while the patient is being rotated on a cradle are very helpful in detecting lesions that can be identified only at certain angles of rotation. The half-axial projection, as recently described by Bunnell et al.,[9] and the sagittal angulated view, as described by Lesperance et al.,[10] are also useful, especially for evaluating the proximal segment of the left coronary artery. A thorough examination of the coronary arterial trees and their lesions through a video recording system before the completion of the procedure is also essential in assuring the adequacy and accuracy of the study.

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Effect of Practolol on Left Ventricular Dimensions During Coronary Occlusion

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Beta adrenergic blockade has been suggested to improve the myocardial oxygen balance during ischemic conditions. This investigation was undertaken to examine the effects of practolol, a relatively cardiospecific beta adrenergic blocking agent, on regional myocardial dimensions and shortening during acute coronary arterial occlusion in dogs. Local myocardial dimensions were measured ultrasonically in ischemic and nonischemic regions of the left ventricle. Myocardial dilatation and marked reduction in systolic shortening occurred in ischemic regions after occlusion, whereas nonischemic regions were only moderately dilated. Administration of 10 to 20 mg of practolol exerted different effects in the two ventricular regions; myocardial dilatation was reduced and the systolic shortening increased by practolol in ischemic regions, whereas further dilatation and diminished shortening occurred in nonischemic control regions. Similar results were obtained when heart rate was kept constant by atrial pacing during beta adrenergic blockade. Thus, practolol improved the function in ischemic ventricular regions, and restored ventricular stroke volume to preocclusion levels, probably as a result of improved myocardial oxygen balance.

Favorable effects of the cardioselective beta adrenergic blocking agent practolol, 4-(2-hydroxy-3-isopropyl amino-propoxy) acetanilide, in patients suffering from acute myocardial infarction have recently been reported.[1] Although this effect might to some extent be attributed to the antidysrhythmic properties of practolol,[2] improvement of the myocardial oxygen balance is suggested from the finding that practolol reduced S-T segment elevation after acute coronary occlusion.[3,4]

Although beta adrenergic blockade is known to cause an overall reduction in myocardial oxygen consumption,[5,6] a concomitant rise in ventricular volume has been demonstrated,[7] which might increase myocardial oxygen demands.[8] However, little is known about the mechanical events in ischemic myocardial tissue as influenced by beta adrenergic blocking agents. Reduced myocardial oxygen supply leads to myocardial dilatation in end-diastole and reduced myocardial shortening.[9] Interventions leading to improved myocardial shortening or reduced ischemic dilatation should thus be regarded as favorable for ventricular function. In this investigation the effects of practolol on myocardial shortening and end-diastolic myocardial dilatation in left ventricular regions acutely deprived of coronary blood supply were studied utilizing ultrasonic measurements of local myocardial dimensions.[10]

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TABLE I

Hemodynamic Effects of Practolol During Coronary Arterial Occlusion in Nine Dogs (mean values ± standard error)

	Control	P_1	During Coronary Occlusion	P_2	During Occlusion with Practolol
LVSP (mm Hg)	115 ± 8	†	109 ± 7	NS	106 ± 7
LVEDP (mm Hg)	2.0 ± 0.3	†	4.8 ± 0.5	†	7.8 ± 0.9
dP/dt (mm Hg/sec)	1480 ± 70	*	1340 ± 70	†	1090 ± 50
SV (ml/beat)	14.6 ± 1.2	*	13.2 ± 1.0	*	14.2 ± 1.2
HR (beats/min)	154 ± 8	NS	155 ± 8	†	133 ± 5

* = P <0.02; † = P <0.005; NS = not significant (P >0.05).

Control = control observations; dP/dt = maximal value of left ventricular pressure rise; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; P_1 = probability value for comparison of paired data obtained before and after coronary occlusion; P_2 = comparison before and after administration of practolol; SV = stroke volume.

TABLE II

Effects of Practolol on Regional Myocardial Dimensions (mm) During Coronary Occlusion

	$EDMCL_{desc}$			SMS_{desc}			$EDMCL_{cf}$			SMS_{cf}		
Dog no.	Control	Occlusion	Occlusion + Practolol	Control	Occlusion	Occlusion + Practolol	Control	Occlusion	Occlusion + Practolol	Control	Occlusion	Occlusion + Practolol
1	9.50	10.00	9.80	0.65	0.40	0.55	11.13	11.48	11.63	0.75	0.80	0.65
2	12.10	12.95	12.75	0.53	0.20	0.27	9.35	9.75	9.85	0.50	0.40	0.30
3	10.40	11.00	11.00	0.50	0.18	0.25	11.65	11.85	11.93	0.65	0.75	0.60
4	10.70	11.10	11.00	0.45	0.35	0.45	11.15	11.45	11.90	0.85	0.78	0.40
5	9.88	10.45	10.45	0.70	0.20	0.25	9.80	10.13	10.55	—	—	—
6	12.05	12.60	12.25	0.65	0.10	0.50	11.50	11.63	12.05	0.60	0.65	0.32
7	10.10	10.60	10.60	0.86	0.40	0.70	11.20	11.45	11.68	0.70	0.85	0.90
8	9.78	11.03	10.80	0.55	0.20	0.28	9.95	10.40	10.65	0.35	0.35	0.33
9	10.66	11.16	11.06	0.50	0.20	0.30	10.50	10.70	10.88	0.65	0.60	0.45
Mean	10.57	11.21	11.08	0.60	0.25	0.39	10.69	10.98	11.24	0.63	0.65	0.49
SEM	0.31	0.32	0.30	0.04	0.04	0.05	0.27	0.25	0.26	0.05	0.07	0.07
P_1		†			†			†			NS	
P_2			*			*			†			*

* = P <0.02; † = P <0.005; NS = not significant (P >0.05).

EDMCL = end-diastolic myocardial chord length in regions supplied by the left anterior descending (desc) and the left circumflex (cf) coronary arteries; SMS = systolic myocardial shortening in these regions; SEM = standard error of the mean. Other symbols and abbreviations as in Table I.

Methods

Animal preparation: Twelve healthy mongrel dogs, weighing 17 to 29 kg, were anesthetized by intravenous administration of sodium pentobarbital, 25 mg/kg body weight, followed by maintenance doses of 50 mg at intervals. The heart was exposed through incision in the fifth left intercostal space, and ventilation maintained by a positive pressure respirator (Cyclator Mk. II, British Oxygen Co., London). The left anterior descending coronary artery was dissected free 0.5 to 2 cm from its origin and a ligature placed loosely around the vessel. Instantaneous myocardial dimensions were measured by ultrasonic transmission between two piezoelectric crystals of lead zirconate titanate (0.5 by 1 by 3 mm) sewn into the left ventricular wall 9 to 11 mm apart at a depth of 5 to 8 mm from the epicardial surface[10]; the frequency response was 40 cycles/sec. The distance between the elements is called myocardial chord length and represents the resultant movement of the muscle fibers between the elements. Provided that postoperative examination showed that myocardial chord length was parallel to the predominating local fiber orientation, high correlation existed between myocardial chord length and thermodilution determinations of left ventricular volume during great variations in ventricular preload and contractility.[10] One pair of elements was placed in the region supplied by the coronary artery to be occluded, and another pair clearly outside this region for control purposes.

Left ventricular pressure was measured by a Statham P23Gb transducer connected to a short catheter introduced through the apex, and the first derivative of left ventricular pressure, dP/dt, was continuously recorded from the pressure channel. Phasic blood flow in the ascending aorta was measured by an electromagnetic flowmeter (Nycotron, model 367, Oslo), and left ventricular stroke volume was determined by beat to beat integration of the flow signals. In three dogs heart rate was kept constant by pacing the right atrium (Grass Instruments model S4G) with pulses of 1 msec at an effective voltage of 1.5 to 2.5 v.

Experimental procedure: After control observations were recorded, the coronary artery was occluded by a May-

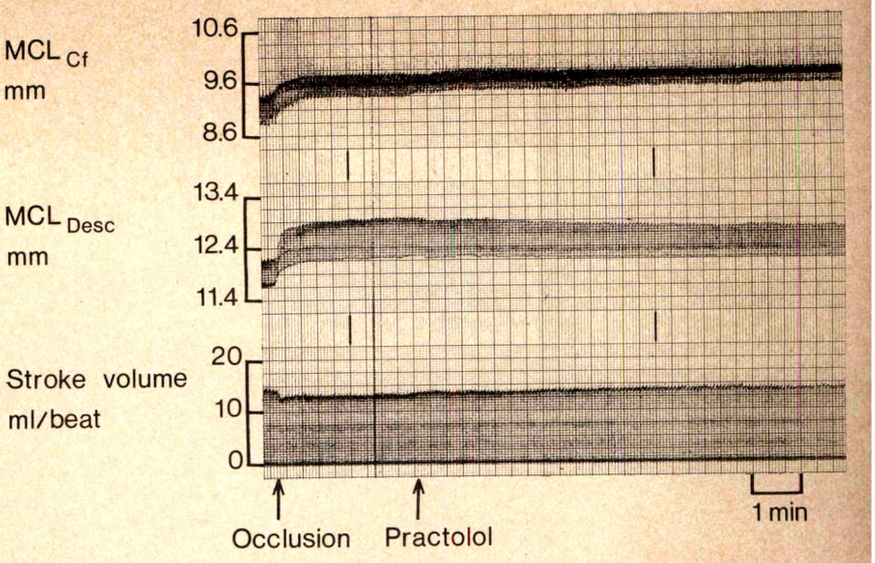

FIGURE 1. Dog 2. Effects of practolol during occlusion of the left anterior descending coronary artery. Recordings of local myocardial chord lengths (MCL) in the ventricular region supplied by the occluded left anterior descending coronary artery (Desc) and by the left circumflex coronary artery (Cf), which was not occluded. Upper margin of tracing denotes the end-diastolic myocardial chord length.

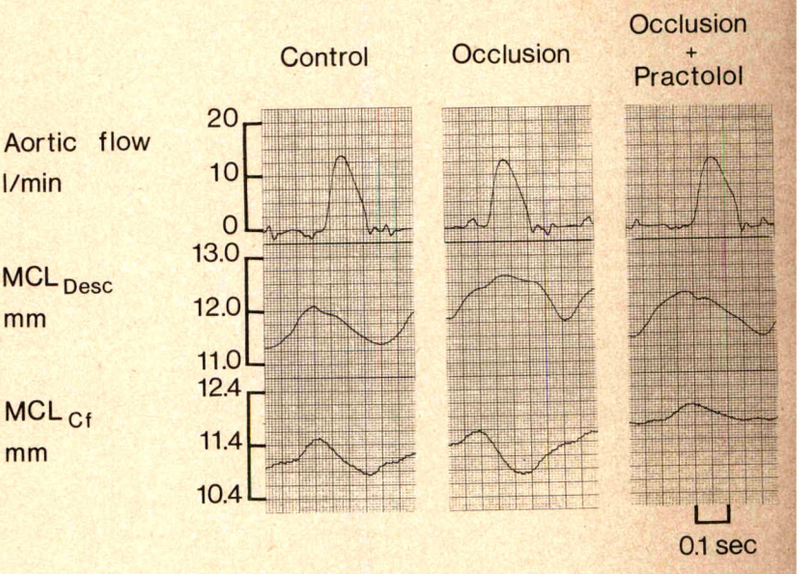

FIGURE 2. Dog 6. Pattern of myocardial shortening during occlusion of the left anterior descending coronary artery before and after administration of practolol. Local myocardial chord lengths (MCL) were recorded in the ventricular region supplied by the descending artery (Desc) and by the nonoccluded left circumflex coronary artery (Cf).

field clip. Redetermination of ventricular dimensions, pressures and flow was performed 3 to 5 minutes after occlusion. Then 10 to 20 mg of practolol (Eraldin, Imperial Chemical Industries, London) was given intravenously over 1 to 3 minutes, and new determinations were made 10 minutes after administration of practolol. All recordings were made during steady hemodynamic conditions.

Immediately after the dogs were killed by administration of an overdose of sodium pentobarbital, Evans blue dye was injected into the coronary artery at the site of former occlusion and colored tissue was isolated and weighed. On average, 34.3 percent of left ventricular weight (range 21.8 to 41.5 percent) had been rendered ischemic by coronary occlusion.

Statistical analysis: Each dog served as its own control. Student's t test for paired data was used to calculate probability values (P).[11] A value of $P > 0.05$ was regarded as not statistically significant.

Results

Tables I and II present the hemodynamic and dimensional effects of coronary arterial occlusion and intravenous administration of practolol in nine dogs with spontaneous cardiac rhythm.

Effects of coronary occlusion: Occlusion of the left anterior descending coronary artery was followed by marked end-diastolic dilatation in regions supplied by this artery (Fig. 1). Myocardial dilatation also occurred in nonischemic control regions supplied by the left circumflex coronary artery, and left ventricular end-diastolic pressure was increased by 2.8 ± 0.5 mm Hg ($P < 0.001$). However, end-diastolic dimensions as estimated by myocardial chord length increased more in ischemic than in nonischemic regions ($P < 0.001$).

A changed contraction pattern of the ischemic myocardium was observed during coronary arterial occlusion. In this part of the left ventricle shortening during ventricular systole was largely reduced (Table II), whereas considerable myocardial shortening occurred in early diastole (Fig. 2). Total amplitude was thus apparently increased in ischemic regions during

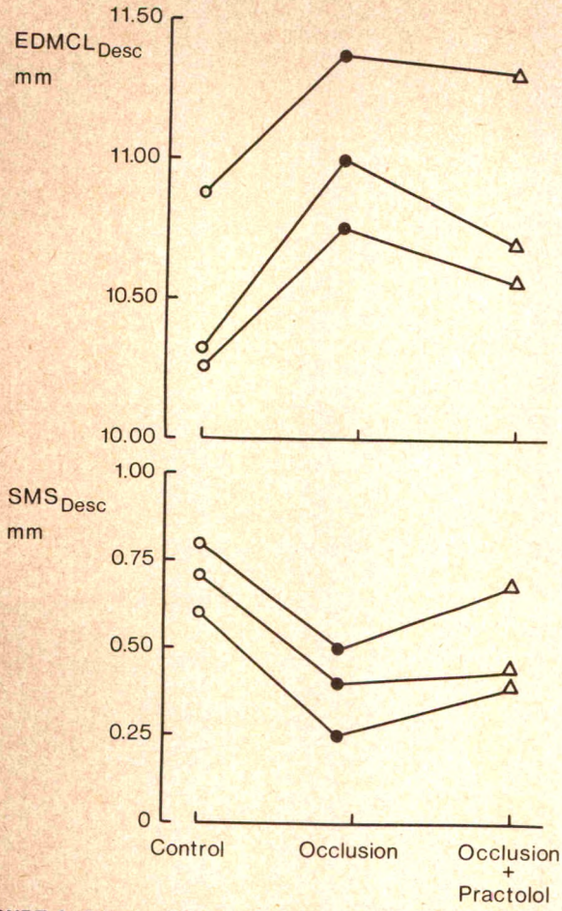

FIGURE 3. Effects of practolol during occlusion of the left anterior descending coronary artery in three dogs with a heart rate kept constant by right atrial pacing. End-diastolic myocardial chord length (EDMCL) and systolic myocardial shortening (SMS) were measured in ventricular regions supplied by the anterior descending artery (Desc).

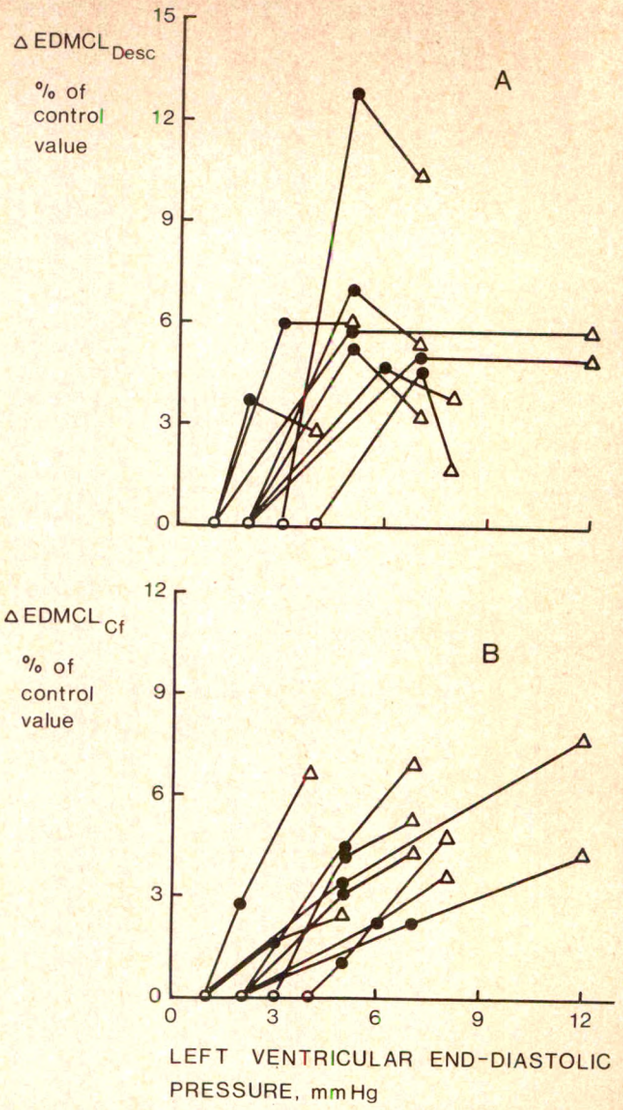

FIGURE 4. Relation between left ventricular end-diastolic pressure and changes in end-diastolic myocardial chord length (ΔEDMCL). **A,** measurements from ventricular regions supplied by the occluded left anterior descending coronary artery (Desc). **B,** measurements from control regions supplied by the nonoccluded left circumflex coronary artery (Cf) Open circles = prior to occlusion; closed circles = during occlusion; triangles = after administration of practolol.

occlusion in most of the experiments (Fig. 1). In nonischemic control regions the systolic myocardial shortening remained unchanged during occlusion.

Left ventricular performance was reduced by coronary occlusion, as evidenced by lower values for stroke volume, cardiac output, dP/dt and left ventricular systolic pressure (Table I).

Effects of practolol: With the coronary artery still occluded, administration of practolol restored stroke volume almost to control levels, although dP/dt was further reduced (Table I). End-diastolic ventricular dimensions in nonischemic regions—and the end-diastolic ventricular pressure—increased further from the values obtained during occlusion alone, whereas the ischemic myocardial dilatation in occluded areas was reduced; however, control levels were not regained during beta adrenergic blockade in any experiment. Practolol diminished the early diastolic myocardial shortening in occluded areas, and a significantly greater portion of shortening occurred in ventricular systole (Fig. 2). In nonischemic regions practolol gave an opposite effect by reducing systolic myocardial shortening (Table II).

Left ventricular systolic pressure remained unchanged during beta adrenergic blockade with practolol. Cardiac output was reduced by 161 ± 47 ml/min ($P < 0.01$) after administration of practolol because the decrease in heart rate was greater than the increase in stroke volume.

In three dogs the heart rate was kept constant (average 141 beats/min) by right atrial pacing. The dimensional measurements are presented separately, and it appears from Figure 3 that the results obtained during administration of practolol were similar to results in the hearts with spontaneous rhythm.

End-diastolic pressure/dimension relation: End-diastolic myocardial chord length in ischemic

regions increased by an average of 6.1 ± 0.9 percent of control value after coronary occlusion, whereas nonischemic chord length increased by only 2.7 ± 0.4 percent (Table II). Although left ventricular end-diastolic pressure was not similarly increased in individual experiments (Fig. 4), the highly significant difference in regional dimensions ($P < 0.001$) indicates a changed pressure/dimension relation in end-diastole during acute myocardial ischemia because ventricular pressures were always identical in the two regions. The reduction of end-diastolic myocardial chord length in occluded regions affected by practolol brought the pressure/dimension curve in these regions close to that obtained in nonischemic ventricular regions (Fig. 5). The measurements therefore indicate that administration of practolol tends to normalize the changed end-diastolic pressure/dimension relation during acute coronary occlusion.

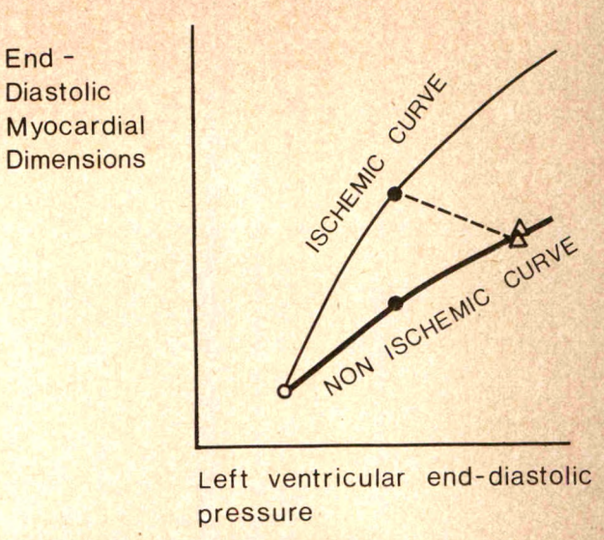

FIGURE 5. Scheme, calculated from the mean values in Figure 4, of the ventricular pressure/dimension relation in ventricular regions rendered ischemic by coronary arterial occlusion and in nonischemic control regions. Open circles = prior to occlusion; closed circles = during occlusion; triangles = after administration of practolol.

Discussion

Practolol and increased systolic myocardial shortening: The most important finding in this investigation was that practolol increased systolic myocardial shortening, which had been largely reduced by coronary occlusion. Although variable effects of practolol on stroke volume and contractility have previously been reported,[4,12] left ventricular dP/dt and systolic myocardial shortening in nonischemic control regions were clearly reduced by practolol in this study. It is therefore reasonable to attribute restoration of stroke volume to an increased myocardial shortening in the ischemic regions. This represents an obvious improvement of ventricular function by practolol during acute coronary occlusion.

Practolol and improved myocardial oxygen balance: It is generally believed that practolol does not increase myocardial oxygen supplies[13] but diminishes net myocardial oxygen requirements through reduction in the contractile state and heart rate,[5,6] although an accompanying ventricular dilatation[7] might increase the myocardial oxygen demands.[8] Recent studies[3,4] have revealed that S-T segment changes after coronary occlusion in dogs and myocardial infarction in patients were reduced by practolol, indicating an improved myocardial oxygen balance. Since a close relation between myocardial oxygen consumption and ventricular dilatation has been demonstrated during graded myocardial ischemia,[9] reduced ischemic dilatation by practolol indicates improved myocardial oxygen balance. A negative chronotropic action of practolol undoubtedly reduces myocardial oxygen demands.[8] However, since improved function of the ischemic myocardium could be demonstrated during constant atrial pacing, reduced end-diastolic dimensions and wall tension[8,9] might also represent a reduction in the myocardial oxygen requirements, thus permitting increased systolic shortening. Thus, in addition to the antidysrhythmic properties of practolol, its ability to improve myocardial oxygen balance through these mechanisms constitutes the rationale for use of this agent in patients with acute myocardial infarction.

Practolol and redistribution of myocardial blood flow: A relative redistribution of coronary blood flow to ischemic areas has been demonstrated after administration of propranolol to hearts with occluded coronary arteries.[14] If such a mechanism also applies to practolol, this could contribute to improved myocardial oxygen balance and function, mainly in ischemic subendocardial layers. The demonstration in this study that improvement of mechanical function within the ischemic third of the left ventricle after beta adrenergic blockade is associated with concomitant reductions of systolic myocardial shortening within the nonischemic two thirds, ventricular contractility as a whole and dP/dt might be explained by redistribution of myocardial blood flow.

Practolol and improved myocardial metabolism: On the other hand, could myocardial oxygen balance also be improved by beta adrenergic blocking agents through metabolic mechanisms? It has been demonstrated that antilipolytic agents reduce S-T segment elevation after acute coronary occlusion,[15] probably by inhibiting myocardial lipolysis evoked by release of endogenous catecholamines in acutely ischemic tissue[16] and leading to a relatively oxygen-expensive consumption of free fatty acids. Antilipolytic activity of practolol has been demonstrated in isolated fat cells[17] and, if this applies also to in vivo myocardial lipolysis, myocardial oxygen requirements might thus be reduced in acutely ischemic myocardial tissue. Furthermore, it has recently been reported[18] that beta adrenergic blockade with propranolol permitted enhanced glycogenolytic energy production during anoxia in rat hearts.

Thus, several mechanisms for improvement of myocardial oxygen balance by beta adrenergic block-

ing agents are proposed although it is not known which is the most important or why oxygen requirements of ischemic myocardial tissue are reduced if increased blood supply may be present. Although these measurements provide no direct information on myocardial oxygen balance, they indicate that the mechanical function of the acutely ischemic myocardium benefits from beta adrenergic blockade by practolol.

Practolol and changes in myocardial compliance: Use of left ventricular end-diastolic pressure measurements to assess cardiac failure has among its limitations dependence on a constant ventricular pressure/volume relation.[19,20] Whereas increased end-diastolic pressure during coronary heart disease is commonly interpreted as an indication of incipient heart failure, the measurements reported here describe a situation after administration of practolol in which improved function of acutely ischemic myocardial tissue is associated with increased ventricular end-diastolic pressure. This finding thus emphasizes the reservations to use of ventricular end-diastolic pressure as a reliable index of ischemia or heart failure. Decreased ventricular compliance has been demonstrated in patients within a few days of myocardial infarction and in patients with chronic coronary artery disease.[21] However, the observations in this study suggest an increased ventricular compliance in end-diastole in the ischemic regions immediately after coronary occlusion. Compliance is defined as dV/dP, where V is volume of the left ventricle and P its intracavitary pressure. Since myocardial chord length increased significantly more within ischemic regions than within control regions, dV/dP must be greater in ischemic areas because the two regions have identical—and increased—ventricular pressures. Although ventricular pressure and dimensions were obtained during steady hemodynamic conditions, they were measured within the time limit of 20 to 30 minutes for development of irreversible cell injury.[22] It is therefore credible that after acute coronary occlusion compliance is initially increased in affected ventricular regions and later decreased, a change that might be explained by the pathologic-anatomic alterations and cell death in the early healing phase.[23] The observations in this study also indicate that practolol normalizes the increased compliance during acute ischemia. This finding implies that the ischemic myocardial tissue becomes capable of operating a more propitious Frank-Starling curve after beta adrenergic blockade, as was indicated by increased systolic shortening and stroke volume ejection after administration of practolol.

Acknowledgment

I thank Mrs. Grethe Laerum and Erik Holgersen, engineer, for their skilled technical assistance, and Mrs. Monica Hyde for help in the preparation and typing of the manuscript.

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Effect of Graded Reductions in Regional Coronary Perfusion on Regional and Total Cardiac Function

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This study examines the effects of graded reduction in regional coronary perfusion and changes in arterial oxygen concentration upon regional myocardial function and left ventricular function. In 14 open chest dogs, the distal left anterior descending coronary artery was cannulated and perfused at different pressures with blood equilibrated with either 21 or 95 percent oxygen, and regional function in the perfused myocardial segment was determined by use of the pressure-length loop. The mass of perfused left ventricular myocardium was determined by injection of sodium fluorescein at a constant pressure of 100 mm Hg. Regional function decreased minimally as coronary perfusion pressure and flow were reduced to 50 to 65 mm Hg and 25 to 55 ml/min per 100 g, respectively. When pressure and flow were reduced below these critical ranges, regional function decreased sharply. Changes in left ventricular function were comparable but of lesser magnitude. The relations between regional function or left ventricular function and coronary perfusion were not affected by changing arterial oxygen concentration, except at the low range of coronary perfusion pressures (22±6 mm Hg), at which pressure regional function was significantly lower ($P < 0.025$) in the experiments with 95 percent oxygen. Thus, the sensitivity of myocardial performance to a decrease in effective coronary perfusion pressure and flow is remarkably dependent upon whether pressure and flow are above a critical level.

Severe coronary arterial stenosis is frequently associated with a reduction in regional blood flow and myocardial ischemia. However, the precise relation between regional coronary perfusion and regional dysfunction is not firmly established. Although it has been shown that a substantial reduction in main left coronary arterial blood flow and perfusion pressure reduces total left ventricular performance,[1–5] insufficient information is available describing regional myocardial function at levels of coronary perfusion that are below normal. These measurements have recently assumed particular clinical relevance with the use of agents that reduce peripheral vascular resistance in the therapy of heart failure due to acute myocardial infarction.[6] Since such agents often reduce coronary perfusion pressure, it is important to know to what extent the perfusion pressure may be decreased before myocardial function in an ischemic area begins to deteriorate.

Although regional coronary perfusion in patients is dependent upon both the aortic pressure and the degree of coronary stenosis, an experimental model in which regional coronary perfusion is carefully controlled may give some insight into the clinical situation. In the experimental animal, regional myocardial function can be studied at various levels of regional coronary perfusion. A sensitive and reproducible method for quantitating regional myocardial contractile function has recently been developed in this laboratory.[7,8] The technique

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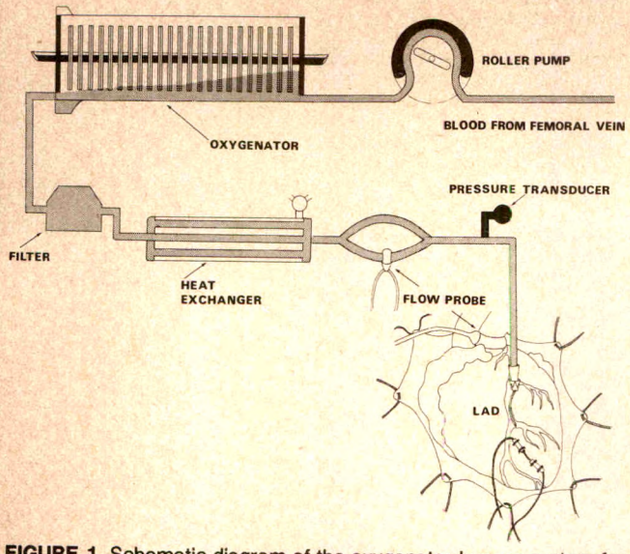


FIGURE 1. Schematic diagram of the oxygenator-bypass system for perfusion of the distal left anterior descending coronary artery (LAD). Blood was withdrawn from the femoral veins, pumped through a disc oxygenator in which the blood was equilibrated with either 21 or 95 percent oxygen, a filter, a heat exchange unit, cannulating electromagnetic flow probe and tap for measurement of perfusion pressure. Coronary perfusion pressure was controlled by adjusting the height of the disc oxygenator.

allows an examination of synchrony of contraction and a quantitation of the mechanical work performed by or dissipated into the myocardial segment under examination. Accordingly, in this study we investigated the relation of regional coronary perfusion to regional myocardial function and left ventricular function during graded decreases in left anterior descending coronary arterial perfusion pressure over a range of 100 to 16 mm Hg. In addition, we studied the effect of high levels of arterial oxygen tension, such as those employed clinically in acute myocardial infarction.

Method

Fourteen mongrel dogs (23 to 27 kg) were sedated with morphine sulfate (2.2 mg/kg body weight, intramuscularly) and anesthetized with ethyl carbamate (1.1 g/kg, intravenously). A left thoracotomy was performed through the fifth intercostal space. Aortic pressure was monitored with a Statham P23Db pressure transducer by means of a catheter passed through the femoral artery. Left ventricular pressure (both low gain and high gain) was recorded by a solid state catheter tip pressure transducer (model BT-7F2, Bio-Tech, Pasadena, Calif.) mounted on a no. 8F double lumen cardiac catheter passed retrograde across the aortic valve. Accuracy of the diastolic pressure determinations was assured by comparison with the magnified pressure wave form recorded from a Statham P23Db external pressure transducer by way of the second lumen. All pressures were referenced to the level of the mid-left ventricle.

A large bore cannula was positioned in the superior vena cava by way of the external jugular vein; a reservoir bottle was connected externally to the cannula and adjusted to the appropriate height to maintain a constant end-diastolic pressure of 5 to 10 mm Hg. Heart rate was not controlled and averaged 140 beats/min in these experiments.

Ascending aortic flow was measured in all experiments and coronary perfusion flow in 10 experiments by means of two electromagnetic flowmeters (model RC 1000, Micron Instruments, Los Angeles, Calif.). The signals were recorded for visual experimentation (Visicorder model 1505, Honeywell, Denver, Colo.) and recorded on magnetic tape for subsequent analysis (model GR-2900, Consolidated Electrodynamic Corporation, Pasadena, Calif.). Left ventricular function was evaluated from the following formula: LVSW = SV × (SP − LVEDP), where LVSW = left ventricular stroke work, SV = stroke volume, SP = mean systolic pressure and LVEDP = left ventricular end-diastolic pressure.

For assessment of regional myocardial function, a 1 cm long mercury-filled Silastic® length gauge (Parks Electronics, Beaverton, Ore.) was fixed in a direction parallel to that of the superficial myocardial fibers and placed within the distribution of the distal left anterior descending coronary artery. The artery was dissected free, cannulated proximal to its last diagonal branch and perfused by an oxygenator-bypass system (Fig. 1). The oxygenator was primed with the experimental dog's blood and removed as blood from a donor dog was transfused. Blood was pumped from the femoral vein with a finger pump into a disc oxygenator that could be raised or lowered to achieve any desired perfusion pressure. To evaluate the effects of high levels of arterial oxygen tension, such as may be employed clinically, the oxygenator was ventilated with gas mixtures containing 5 percent carbon dioxide and 21 or 95 percent oxygen, resulting in arterial oxygen partial pressures of 100 and 300 mm Hg, respectively. A filter, cannulating electromagnetic flow probe, heat exchanger and tap for measurement of perfusion pressure completed the circuit.

Regional myocardial function was evaluated using the pressure-length loop method previously described by this laboratory.[7,8] When left ventricular pressure is plotted simultaneously against epicardial segment length, a "pressure-length loop" is obtained that closely resembles the pressure-volume loop of the intact heart. The area within the pressure-length loop is an index of the work performed by or on the myocardial segment, and has been shown to correlate closely with total cardiac function during alterations in preload, afterload, contractility and heart rate.

Experimental Procedure

In each experiment, immediately after coronary cannulation, perfusion of the distal half of the left anterior descending coronary artery was continued at a perfusion pressure of approximately 100 mm Hg for at least 20 minutes. After this initial stabilization period, perfusion pressure was reduced in stepwise fashion with a return to the initial level (100 mm Hg) after each step. Each step consisted of a reduction in perfusion pressure of approximately 7–10 mm Hg that was maintained for 2 minutes, a period that previous studies[7,9] have indicated should permit stabilization of hemodynamics under ischemic conditions. This procedure was continued until a range of perfusion pressures between 100 and 16 mm Hg was obtained.

Finally, the heart was removed and sodium fluorescein was injected into the distal left anterior descending coronary artery by means of the perfusion cannula at a constant pressure of 100 mm Hg. The left ventricular myocardium was separated into stained and unstained portions by examination under ultraviolet light, and each portion was

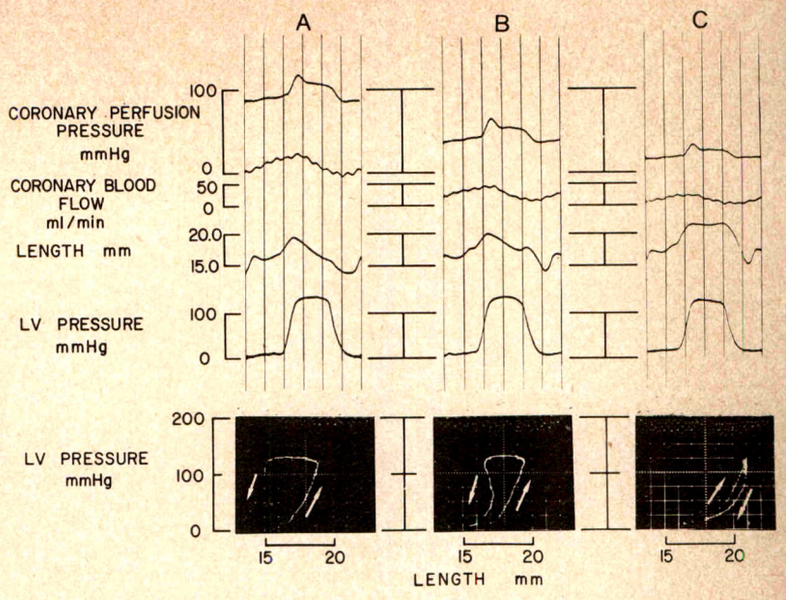


FIGURE 2. Effect of graded reductions in coronary perfusion pressure on coronary blood flow, epicardial segment length in the perfused regional myocardium, aortic and left ventricular (LV) pressures, and the relation between left ventricular pressure and epicardial segment length in a representative experiment in which the blood perfusate was saturated with 21 percent oxygen. **A,** normal systolic contraction. **B,** decrease in systolic shortening. **C,** systolic dyskinesis in ischemic segment. (See text.)

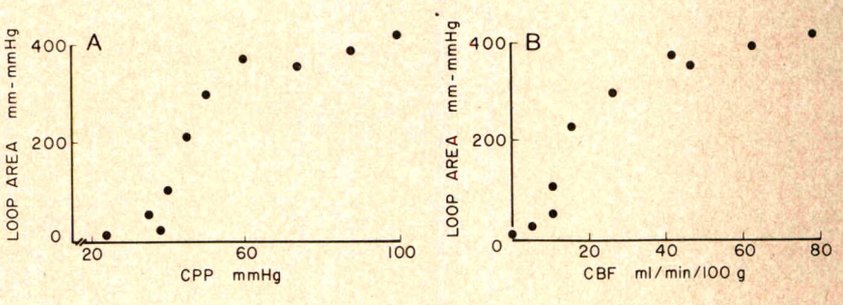


FIGURE 3. A, relation between coronary perfusion pressure (CPP) and the area of the pressure-length loop, an index of regional myocardial function, in a representative experiment. **B,** relation between coronary blood flow (CBF) and area of the pressure-length loop in the same experiment. (See text.)

weighed separately to estimate the amount of left ventricular myocardium perfused experimentally by the external circuit.

Although fluorescein has previously been used as a stain for the myocardium,[10] its use had certain limitations in this study. Injection of fluorescein was performed at the control pressure of 100 mm Hg and the stained area should represent the area of myocardium perfused during the control period. However, in this study, when coronary perfusion pressure was reduced over a range of pressures, the area of perfused myocardium may have changed accordingly. Therefore, there may be some error in the estimate of perfused area for coronary perfusion pressures below the control level of 100 mm Hg.

Data Analysis

Analysis of myocardial segment function was performed as follows: Coronary perfusion pressure levels were divided arbitrarily into seven ranges of 12 mm Hg each: 88 to 100, 76 to 87, 64 to 75, 52 to 63, 40 to 51, 28 to 39 and 16 to 27 mm Hg. Within each range of coronary perfusion pressure, a mean pressure-length loop area was determined. The mean area within the highest common pressure range, 64 to 75 mm Hg, was arbitrarily chosen as the control value (100 percent segment function); at any given pressure range, segment function was calculated as percent of mean loop area with respect to control loop area. Analysis of left ventricular function was performed similarly on the basis of values for left ventricular stroke work. From the perfusion pressure (CPP) and flow (CBF) data, the resistance to flow ("bed resistance") was calculated for each data point as r = CPP/CBF.

Results

Regional Myocardial Function

Figure 2 illustrates typical data obtained from an experiment in which the left anterior descending coronary artery was cannulated and perfused with blood equilibrated with 21 percent oxygen. In the control state (Fig. 2A) at a perfusion pressure of 95 mm Hg and a coronary blood flow rate of 99 ml/min per 100 g, the typical pressure-length loop was counterclockwise and completely normal with respect to the loop recorded before cannulation. Two minutes after reduction of coronary perfusion pressure to 47 mm Hg (Fig. 2B) and coronary blood flow to 21 ml/min per 100 g, there was a characteristic change in the length tracing consisting of late systolic lengthening and delayed shortening. The result was a decrease in the area of the pressure-length loop and the characteristic shape shown. Two minutes after reduction of the perfusion pressure to 22 mm Hg (Fig. 2C) and coronary flow to −4 ml/min per 100 g, the length tracing demonstrated epicardial segment lengthening throughout most of systole and shortening only at

pressures near the diastolic level. The pressure-length loop was inscribed in a clockwise direction, and the value for loop area was negative, indicating that work was expended in stretching the segment.

Figure 3 shows the relation of coronary perfusion pressure and coronary blood flow to the area of the pressure-length loop in a typical experiment in which the coronary perfusion blood was saturated with 21 percent oxygen. As coronary perfusion pressure was reduced from 100 to 50 to 60 mm Hg and coronary flow from 80 to 30 to 40 ml/min per 100 g, the loop area decreased to approximately 85 percent of the initial value. When pressure and flow continued to decrease, however, loop area decreased rapidly to approximately zero. In this experiment, the critical levels of coronary pressure and flow below which segment function decreased rapidly were 50 to 60 mm Hg and 30 to 40 ml/min per 100 g, respectively.

Relation of coronary perfusion pressure to segment function: Figure 4A illustrates this relation in 16 experiments, comparing the effects of 21 percent oxygen saturation (arterial PO_2 100 mm Hg) to 95 percent oxygen saturation (arterial PO_2 300 mm Hg). In the experiments with 21 percent oxygen saturation, as coronary perfusion pressure was reduced from the high range, 88 to 100 mm Hg, to a middle range, 52 to 63 mm Hg, segment function decreased at a rate of approximately 0.7 percent per mm Hg. As perfusion pressure was reduced below 52 to 63 mm Hg, segment function decreased rapidly at a rate of about 2.5 percent per mm Hg, to a value of zero at a range of perfusion pressures of 16 to 27 mm Hg. In the experiments with 95 percent oxygen saturation, segment function decreased in a parallel fashion except for a slight but significant enhancement of function in the range of 76 to 87 mm Hg. However, at the lowest level of perfusion pressure, segment function was reduced to a mean value that was significantly lower ($P < 0.02$) than that in the experiments with 21 percent oxygen saturation. The linear relation between perfusion pressure and flow in Figure 4B suggests that coronary resistance was minimal in each dog, even at the control levels of perfusion pressure (95 mm Hg); that is, there was no autoregulation in the coronary bed. Although normal segment function was present in the control state after coronary cannulation, the experimental procedure of cannulation may have caused the loss in autoregulatory capacity by producing a state of mild ischemia in which flow and function were preserved by autoregulation.

Coronary bed resistance: Coronary bed resistance (r = CPP/CBF), calculated in 14 dogs, ranged from 0.7 to 3.9 units. Since pH may affect vascular distensibility but was not controlled in this study, the variability in pH may have contributed to the wide range of coronary vascular resistance levels. Another possible cause of this variation in resistance values may have been release of vasodilator substances when blood of the donor dog was mixed with blood of the experimental dog. However, despite the wide range of values, there was a critical level of coronary blood flow in the narrow range of 25 to 55 ml/min per 100 g, below which function was markedly impaired (Fig. 5).

Relation between coronary blood flow and segment function: Figure 5 illustrates the individual relation between segment function and coronary blood flow (ml/min per 100 g) for five experiments with 95 percent oxygen saturation and five experiments with 21 percent oxygen saturation. There is

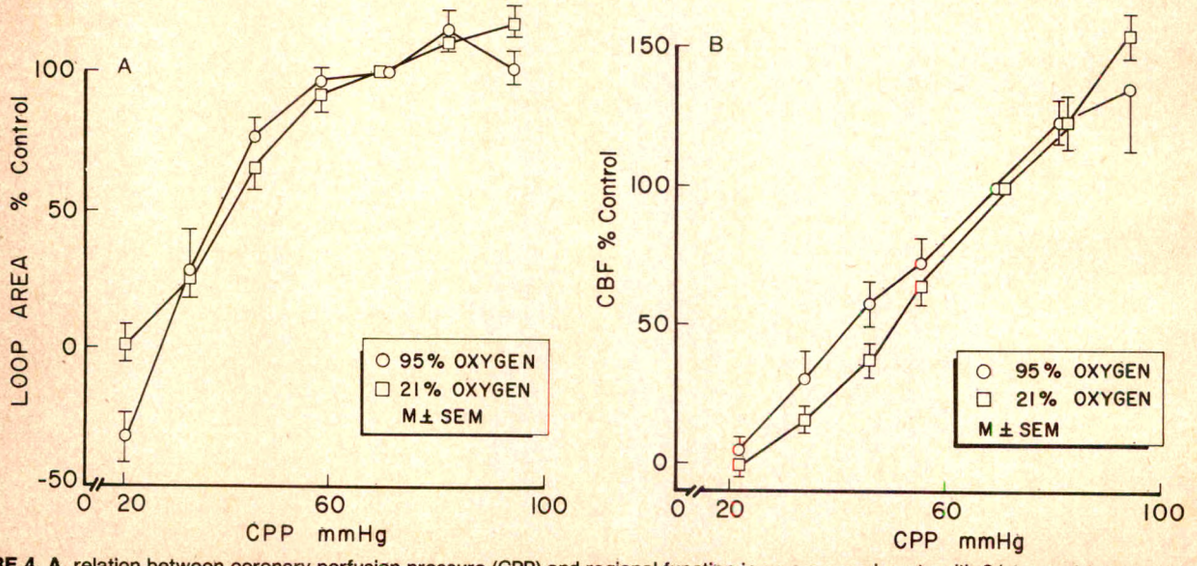


FIGURE 4. A, relation between coronary perfusion pressure (CPP) and regional function in seven experiments with 21 percent oxygen saturation (**squares**) and nine experiments with 95 percent oxygen saturation (**circles**). Regional epicardial function was determined as the pressure-length loop area in percent of control level (at a perfusion pressure of 70 ± 6 mm Hg) and plotted as the mean value ± 1 standard error of the mean. **B,** relation between coronary perfusion pressure (CPP) and coronary blood flow (CBF) for five experiments with 21 percent oxygen saturation (**squares**) and five experiments with 95 percent oxygen saturation (**circles**). Coronary blood flow was determined as a percent of control (at a perfusion pressure of 70 ± 6 mm Hg) and plotted as the mean value ± 1 standard error of mean. (See text.)

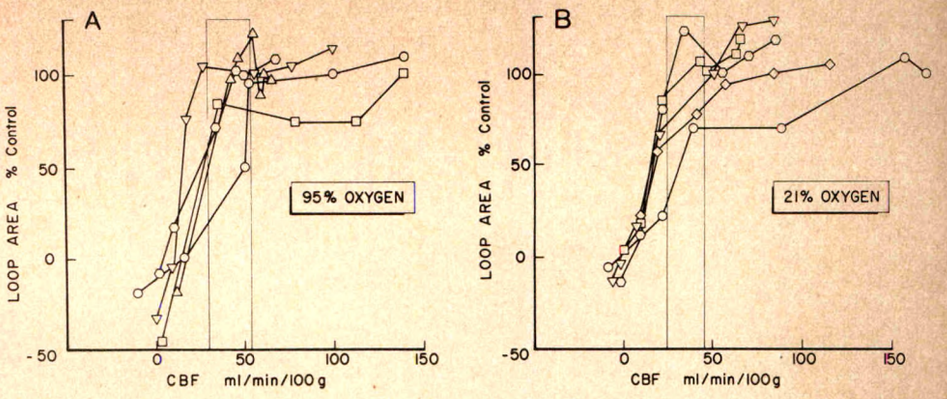


FIGURE 5. Individual relation between coronary blood flow (CBF, ml/min per 100 g) and regional epicardial function for five experiments with 95 percent oxygen saturation (**A**) and five experiments with 21 percent oxygen saturation (**B**). The **vertical lines** through each plot indicate the approximate critical ranges of coronary blood flow below which regional function declined sharply. The critical range was 30 to 55 ml/min per 100 g in **A**, and 25 to 45 ml/min per 100 g in **B**.

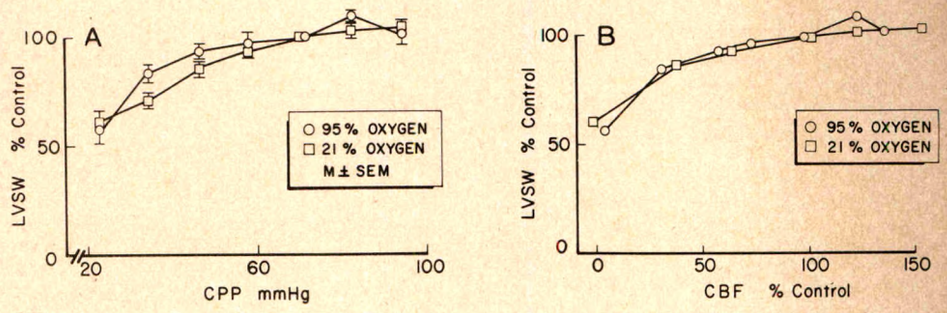


FIGURE 6. A, relation between coronary perfusion pressure (CPP) and left ventricular stroke work (LVSW) for seven experiments with 21 percent oxygen saturation (**squares**) and nine experiments with 95 percent oxygen saturation (**circles**). **B,** relation between coronary blood flow (CBF) (ml/min per 100 g) and left ventricular stroke work for five experiments with 21 percent oxygen saturation (**squares**) and five experiments with 95 percent oxygen saturation (**circles**). Left ventricular stroke work (LVSW) was determined as percent of control (at a perfusion pressure of 70 ± 6 mm Hg) and is plotted as the mean value ± 1 standard error of the mean. (See text.)

some individual variation in this relation, but it is evident that the ranges of flow within which segment function began to deteriorate were 30 to 55 ml/min per 100 g in the experiments with 95 percent oxygen saturation and 25 to 45 ml/min per 100 g in the experiments with 21 percent oxygen saturation. At higher flow ranges, segment function was well maintained, and at lower ranges segment function greatly deteriorated. Retrograde flow was more often observed in experiments with 21 percent oxygen saturation (Fig. 5).

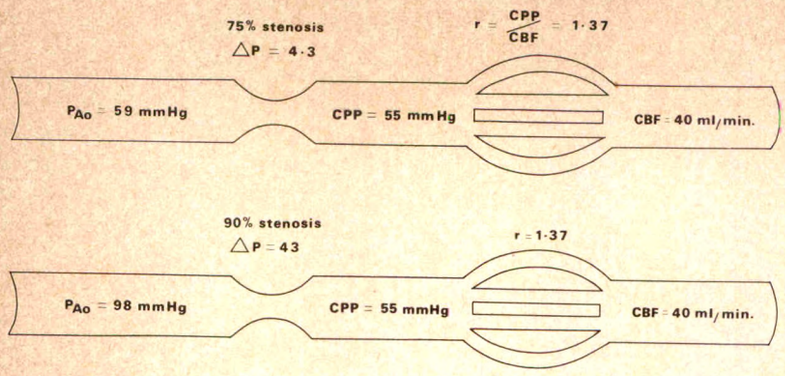
Left Ventricular Function

Figure 6 illustrates the effects of coronary perfusion pressure and flow on left ventricular function. As pressure was decreased from the highest levels to 52 to 63 mm Hg and flow decreased to 40 to 50 percent of control values, left ventricular stroke work decreased gradually. However, in the experiments with 95 percent oxygen saturation, there was an initial enhancement of left ventricular stroke work similar to the enhancement of segment function seen at the same pressure and flow levels. Below the critical level of coronary perfusion pressure, 52 to 63 mm Hg, segment function began to decrease rapidly, reaching maximal rates of 2.1 percent per mm Hg with 95 percent oxygen saturation and 1.3 percent per mm Hg with 21 percent oxygen saturation. At the lowest levels of coronary pressure and flow, left ventricular stroke work had decreased to 60 percent of the control value, thus suggesting that approximately 40 percent of the total left ventricular function in control conditions was lost by reducing to almost zero the flow to a segment of the myocardium.

Discussion

Myocardial segment function examined by pressure-length loop: In this study, segment function was measured in a myocardial region during controlled coronary perfusion in the distal left anterior descending coronary artery. Any changes in coronary flow or regional function that may have occurred outside the region of controlled perfusion were not measured. Segment function was analyzed by means of the pressure-length loop method, a technique developed in this laboratory.[7,8]

The pressure-length loop provides a sensitive means of examining the synchrony of contraction of a given segment with respect to the total left ventricle. Left ventricular pressure reflects the time course of contraction in the mass of normal myocardium, whereas regional segment length reflects the time course of contraction of the ischemic segment interacting with adjacent normal myocardium. Interestingly, the progression of segment length changes during stepwise reduction of coronary perfusion in



	75% stenosis	90% stenosis
CPP	55 mmHg	55
CBF	40 ml/min.	40
Required P_{Ao}	59 mmHg	98
Pressure drop	4·3 mmHg	43
Resistance (r)	1·37 units	1·37

FIGURE 7. Schematic illustration of the effect of proximal coronary arterial stenosis on the aortic perfusion pressure (P_{Ao}) required to maintain a distal coronary perfusion pressure (CPP) of 55 mm Hg and coronary blood flow (CBF) of 40 ml/min per 100 g for two stenoses of 75 and 90 percent. (See text.) ΔP = change in pressure.

this study (Fig. 2) closely resembles the time course of changes in segment length in an ischemic region after coronary occlusion, as described in a previous study from this laboratory.[7] The segment length first began to lengthen late in systole; this lengthening occurred progressively earlier until there was little or no shortening during systole. These changes represent a progressive decrease in capacity of the ischemic muscle segment to shorten during systole against the stress developed by normal segments of the left ventricle.

The area enclosed by the pressure-length loop, inscribed over the entire course of one cardiac cycle, tends to reflect the net mechanical work of the myocardial segment during that cycle.[7,8] A segment that contracts during systole produces a positive loop area; one whose contraction is negated by expansion produces a zero loop area; and one that shortens at a lesser pressure than that at which it lengthens produces a negative loop area. Thus, the relative magnitude of energy that the heart loses with an expanding ischemic segment is represented by the area of the clockwise (that is, negative) pressure-length loop. In this manner, regional myocardial function is evaluated during stepwise reduction of coronary perfusion.

Coronary perfusion pressure and flow and regional myocardial function: Our study indicates that the effect of a given reduction in regional coronary perfusion pressure and flow upon regional myocardial function is critically dependent upon the preexisting levels of pressure and flow. Thus, substantial reductions in perfusion pressure, from 100 to approximately 55 mm Hg, were accompanied by a small reduction in regional function, whereas reduction in pressure below the narrow range of 65 to 50 mm Hg resulted in substantial reduction in the function of the ischemic segment. In addition, our study demonstrates that the reduction in regional function is translated into comparable reductions of lesser magnitude in left ventricular performance.

Our results are in agreement with those obtained by other investigators[11–15] who found that cardiac contractile performance varies directly but minimally with coronary perfusion pressure in the normal physiologic range. Our data suggest that the approximate lower limits of the so-called normal physiologic range for coronary flow and pressure are approximately 55 to 25 ml/min per 100 g and 65 to 50 mm Hg, respectively. Below these levels, regional myocardial function deteriorated three to five times more sharply than at the higher, more physiologic levels of pressure and flow. Changes in left ventricular stroke work paralleled those of regional myocardial function but were smaller. These data are in close agreement with those of Lekven et al.,[5] who found that total cardiac function was impaired when perfusion pressure in the main left coronary artery was less than 50 to 60 mm Hg.

Subendocardial vs. epicardial segmental function: Since the subendocardium is more vulnerable than the epicardium to ischemia,[16] it is possible that the relation of function in the subendocardium to coronary perfusion may be different from the relation found in our study between epicardial segment function and coronary perfusion (especially the critical levels of flow and perfusion). Lekven et al.[5] used ultrasonic micrometer measurements to evaluate changes in left ventricular subendocardial end-diastolic segment length. Although their studies did not quantitate regional systolic performance in the manner described in this investigation, replotting of their instantaneous subendocardial segment length and

left ventricular pressure data from a single experiment reveals that at coronary perfusion pressures of less than 55 mm Hg, subendocardial segment function decreased markedly. These data suggest that the same critical levels of coronary perfusion pressure found in our study for epicardial segment function are applicable to subendocardial segmental function.

High oxygen concentrations and regional myocardial ischemic function: Our study demonstrates that administration of high oxygen concentrations has little effect on regional ischemic myocardial function. Although oxygen administration increases arterial oxygen tension from 100 to 300 mm Hg, oxygen delivery is not increased much because almost complete saturation of hemoglobin normally occurs at an oxygen tension of 100 mm Hg. It is possible that the gradient for oxygen transfer is improved by high levels of arterial oxygen tension. However, at the lowest levels of coronary perfusion pressure, mean segment function was significantly lower ($P < 0.02$) in the experiments with 95 percent oxygen saturation, and retrograde flow was most often observed in the experiments with 21 percent oxygen saturation. At the lowest levels of coronary perfusion pressure, the mean loop area was approximately zero for the experiments with 21 percent oxygen, indicating that no effective work was produced in the ischemic region; in the experiments with 95 percent oxygen saturation the mean loop area was approximately −35 percent of the control value, indicating a dissipation of energy into the dyskinetic ischemic segment. Although these observations may have been the result of individual variations in collateral circulation, it is also possible that 95 percent oxygen concentrations may reduce flow through collateral vessels to the ischemic region and thus reduce contraction in these regions.

Applications to clinical coronary artery disease: The following example demonstrates the clinical usefulness of the combined data from this study and another study performed in this laboratory.[17] The critical levels of regional coronary perfusion pressure and flow, 50 to 65 mm Hg and 25 to 55 ml/min per 100 g, respectively, are analogous to the critical pressure and flow levels distal to a coronary stenosis in a patient with coronary artery disease. If the size of the stenosis is known, the aortic diastolic pressure necessary to maintain regional myocardial function can be calculated as schematically illustrated in Figure 7. The decrease in pressure across stenotic fresh postmortem human coronary arteries was measured at various flow rates and perfusion pressures.[17] Two hemodynamically significant stenoses, 75 and 90 percent, are represented. The coronary flow and pressure distal to both stenoses were identical, that is, in the range of the minimal pressure and flow necessary to maintain regional myocardial function, as determined in this study (coronary perfusion pressure = 55 mm Hg and coronary blood flow = 40 ml/min for 100 g of perfused tissue). At a coronary blood flow rate of 40 ml/min, the measured reductions in pressure across the two stenoses were found to be 4.3 mm Hg for the 75 percent stenosis and 43 mm Hg for the 90 percent stenosis. Thus, to maintain coronary perfusion pressure at 55 mm Hg distal to a 75 percent stenosis, an aortic diastolic pressure of 59.3 mm Hg would be required whereas, if a 90 percent stenosis were present, the required aortic diastolic pressure would be 98 mm Hg. In the latter situation, maintenance of aortic pressure at high levels would be critical for maintenance of useful function in myocardium beyond the coronary stenosis.

The missing links in the clinical application of this knowledge are the capabilities for determining the precise degree of coronary stenosis and the mass of myocardium perfused by the affected vessel. Once these capabilities are obtained, determination of the critical level of aortic diastolic pressure necessary to maintain regional myocardial function will be possible in patients with coronary disease. This will be an important step in the clinical management of such patients, especially since the use of agents that decrease arterial blood pressure is becoming more widespread.

From these data, therefore, two hypotheses may be proposed for the relation between regional blood flow, pressure and function in clinical coronary artery disease. First, the magnitude of deterioration in regional function that accompanies a reduction in regional blood supply is probably curvilinear in nature; only a small decrease in function occurs until a critical flow level is reached, after which a substantial reduction in function accompanies a minimal reduction in flow. Second, although the administration of oxygen may be justified in an attempt to reduce infarct size, it may have little effect upon the relation between regional flow and function.

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Diastolic Compliance of the Left Ventricle in Man

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Two coordinates of left ventricular end-diastolic pressure (P) and volume (V) were provided by the infusion of angiotensin in 22 patients. The slope (k) of the ln P-V relation, coupled with knowledge of the operating (end-diastolic) pressure allows determination of end-diastolic volume compliance (dV/VdP). Estimates of end-diastolic compliance from a single coordinate of pressure and volume compared well (r = 0.90) with the two coordinate method, whereas values for specific compliance ($\Delta V/V_i \Delta P$) appeared to be misleading in cases of idiopathic hypertrophic subaortic stenosis and congestive cardiomyopathy. Since volume compliance is determined in part by the operating pressure, compliance may be reduced in small, normal or enlarged ventricles.

Left ventricular linear compliance was derived from volume compliance and was normalized for left ventricular wall thickness. The product of linear compliance and end-diastolic stress provides an index of myocardial strain, termed "muscle fiber stretch," which may be related to systolic performance and thus allow comparison of length-performance relations in ventricles with normal and abnormal compliance.

Meaningful interpretation of left ventricular end-diastolic pressure in the analysis of ventricular function can be made only when the relation between filling pressure and end-diastolic volume is known. Several investigators using different methods and assumptions have determined diastolic pressure-volume relations in man and have estimated diastolic compliance. These measurements have been utilized to aid in interpreting standard ventricular function curves,[1] gain prognostic information,[2] investigate the increase in ventricular filling pressure observed during angina pectoris[3] and estimate relative sarcomere length at end-diastole in diseased ventricles.[4] In this study, serial heterometric changes were produced (using infusion of angiotensin) to provide two coordinates of left ventricular end-diastolic pressure and volume, and these two coordinates were plotted as the natural logarithm of pressure (ln P) vs. volume. The slope of this (ln P-V) relation and knowledge of the operating (end-diastolic) pressure allow estimation of left ventricular end-diastolic compliance, which in turn may be related to (1) increased pulmonary venous pressure and consequent dyspnea, or (2) abnormal utilization of the Starling mechanism with consequent alterations in systolic performance, or (3) both.

Methods

Patients

Hemodynamic studies were performed in 22 patients undergoing diagnostic cardiac catheterization. Five patients, studied to evaluate a cardiac

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murmur or chest pain, had normal hemodynamic and angiographic findings. Eight patients had coronary artery disease with angina pectoris and various degrees of left ventricular asynergy. Five patients with normal coronary arteriograms had the essential clinical and hemodynamic manifestations of congestive cardiomyopathy as described by Goodwin.[5] A fourth group consisted of four patients with marked left ventricular hypertrophy, two with severe valvular aortic stenosis and two with the typical clinical, hemodynamic and angiographic findings of idiopathic hypertrophic subaortic stenosis. All 22 patients had normal sinus rhythm and only 1 (Case 21) had mild mitral regurgitation.

Hemodynamic Studies

All patients underwent cardiac catheterization in the fasting state after premedication with diazepam, 10 mg intramuscularly. Pressures were measured with no. 8F catheters connected to Statham P23Db pressure transducers from a zero reference point at mid-chest level. An Electronics for Medicine photographic recorder was utilized. The left ventricular end-diastolic pressure was taken as the junction of the downslope of the *A* wave with the upstroke of the ventricular pressure wave; the end-diastolic and end-systolic volumes were determined using single plane cineangiography and the area-length method. Wall thickness was determined as the average thickness of the middle third of the left ventricular free wall as visualized cineangiographically (right anterior oblique projection).[6] The systolic ejection fraction was derived as the angiographic stroke volume divided by the end-diastolic volume. Ventricular premature contractions and the beats following the premature beats were excluded from analysis. All cineangiographic measurements were corrected for magnification and all volumes expressed in cubic centimeters per square meter of body surface area.

In each case, resting hemodynamic measurements and a left ventricular cineangiogram (right anterior oblique projection) were obtained before infusion of angiotensin. Angiotensin was infused (0.5 mg/250 cc of 5 percent dextrose in water) at a rate sufficient to produce a distinct pressor response and an increase in end-diastolic pressure. Five to 6 minutes after achievement of a steady state, left ventricular pressure was measured and a second ventriculogram was obtained and analyzed in the manner outlined. No patient complained of angina or dyspnea during angiotensin infusion.

Diastolic Properties of Left Ventricle

The diastolic properties of the left ventricle were evaluated by a method similar to that employed in animals by McCullagh et al.[7]; in their studies, several coordinates of end-diastolic pressure and end-diastolic dimension were obtained over a range of end-diastolic pressures produced by volume expansion or controlled hemorrhage. Pressures were plotted against dimensions and the pressure-dimension relation was defined by employing a linear analysis of the data.

In this study, two coordinates of left ventricular end-diastolic pressure (P) and volume (V) were obtained (control period and angiotensin infusion) and, assuming an exponential relation between end-diastolic pressure and volume, a modulus or coefficient of volume compliance was derived as the slope (k′) of the ln P-V relation (ln P = natural logarithm of the end-diastolic pressure). The slope (k′) was calculated as:

$$k' = (\ln Pa - \ln Pc)/(Va - Vc) \quad (1)$$

where Pa and Va = end-diastolic pressure (mm Hg) and end-diastolic volume (cc/m^2) during infusion of angiotensin, and Pc and Vc = end-diastolic pressure (mm Hg) and end-diastolic volume (cc/m^2) during the control period. Additionally, the pressure intercept (b′) at zero volume was obtained in every case by linear extrapolation of a line joining the two coordinates of ln P and V. Although extensive data in man are lacking, isolated cardiac muscle length-tension relations[8] and canine pressure-volume relations[9] are easily fit by an exponential function, and thus we elected to analyze our data on the basis of exponential relation between pressure and volume at end-diastole. Preliminary studies in our laboratory suggest that although dynamic components of the in vivo human diastolic pressure-volume relation produce minimal deviations from the elastic (exponential) curve, pressure and volume can be fit by an exponential function.[10] Visual inspection of these curves, in fact, suggests that the data are better fit by a curvilinear than by a linear equation.

An index of end-diastolic volume distensibility (dV/dP), defined as the inverse slope of a tangent to the pressure-volume curve at end-diastole, may be calculated as:

$$(dV/dP)_{ed'} = 1/k'P \quad (2)$$

and end-diastolic volume compliance, likewise may be calculated as (dV/dP)ed′ normalized for end-diastolic volume:

$$(dV/VdP)_{ed'} = 1/k'P \cdot 1/V \quad (3)$$

where P = control end-diastolic pressure, V = control end-diastolic volume and k′ = the slope of the ln P-V relation as defined in equation 1.

A similar, but simplified, method of evaluating left ventricular diastolic volume compliance was also employed. This method, which utilizes a single coordinate of end-diastolic pressure and volume and a constant pressure intercept (b) of 0.43 mm Hg, assumes that the end-diastolic pressure-volume relation can be represented as:

$$P = be^{kV} \quad (4)$$

where e = the base of the natural logarithm. This equation can be rearranged and rewritten as:

$$k = (\ln P - \ln 0.43)/V \quad (5)$$

Thus, left ventricular (dV/dP)ed and (dV/VdP)ed may be calculated as 1/kP and 1/kP·1/V, respectively. Note that k (equation 5) is derived from a single measured coordinate of pressure and volume, whereas k′ (equation 1) is derived from two measured coordinates of pressure and volume. The theory and derivations of these formulas have previously been outlined in detail,[4,11] and the basic assumptions have been utilized in clinical studies.[3,12,13]

"Specific compliance" was determined by relating the total diastolic increase in volume to the diastolic increase in pressure, and the value was normalized by initial volume as described by Smith et al.[14] This method of estimating diastolic compliance describes an average relation between pressure and volume throughout diastole and is calculated as:

$$SC = \Delta V/\Delta P \cdot 1/V_i \quad (6)$$

where ΔV = average stroke volume (cc/m^2), ΔP = the difference between left ventricular end-diastolic pressure and the lowest pressure recorded in early diastole (mm Hg) and V_i = end-systolic volume (cc/m^2). The units of specific compliance (l/mm Hg) are the same as the units of (dV/VdP)ed.

Left ventricular end-diastolic stress and peak systolic stress were estimated utilizing a method previously described in detail.[4] The basic calculations were made using the formula of Sandler and Dodge[15]; the stresses derived represent mean circumferential wall stresses and are expressed in 10^3 dynes cm^2. Peak developed systolic stress was determined as the peak systolic stress minus end-diastolic stress. A work index of the ventricle was provided by the product of peak developed stress and stroke index and is expressed in units of 10^5 dyne/cm.

Determinants of left ventricular end-diastolic fiber strain include not only the force acting to lengthen the fiber (end-diastolic stress), but also the passive resistance to stretch (parallel elasticity or linear compliance). Thus an index of end-diastolic fiber strain is provided by the product of end-diastolic stress and end-diastolic compliance.[4] End-diastolic volume compliance (equation 3) was obtained from volume data, and an estimate of linear muscle compliance, corrected for wall thickness (h), was derived as:

$$\text{Linear compliance (cm/mm Hg)} = 1/3 \cdot dV/VdP \cdot h \quad (7)$$

This estimate is made assuming a spherical left ventricle and results in an under-estimation of linear compliance (which is of greater magnitude in idiopathic hypertrophic subaortic stenosis than in congestive cardiomyopathy). More precise determination of linear compliance at the minor axis (b) of the ventricle would be provided by the approach of Battle et al.,[16] which defines db/bdP using a prolate spheroid as a model. Linear muscle fiber stretch (LMFS) is calculated as:

$$\text{LMFS} = \text{Linear compliance} \cdot \text{LVED stress} \quad (8)$$

where LVED = left ventricular end-diastolic.

Muscle fiber stretch, an index of muscle strain, is expressed in arbitrary units, and results are expressed as averages ± 1 standard error of the mean.

Results

Left ventricular end-diastolic pressure-volume relations: Hemodynamic and angiographic data on all 22 patients are presented in Table I. During the control period, the average left ventricular end-diastolic volume of the patients with coronary artery disease (86 ± 9 cc/m^2) did not differ significantly from the average for the normal group (75 ± 8 cc/m^2). The patients with cardiomyopathy had an average end-diastolic volume (101 ± 13 cc/m^2) that was significantly greater ($P = 0.05$) than normal. Although the average end-diastolic volume in the group with hypertrophy (55 ± 11 cc/m^2) was less than normal, the difference did not achieve statistical significance.

The average end-diastolic pressure during the control period of the group with coronary artery disease (14.9 ± 1.8 mm Hg) was greater ($P < 0.02$) than the average of the normal group (8.2 ± 1.2 mm Hg). The average end-diastolic pressure of the group with hypertrophy (15 ± 2.5 mm Hg) was significantly greater ($P < 0.05$) than normal, whereas the average of the group with cardiomyopathy (10.7 ± 2.6 mm Hg) did not differ significantly from normal. The low level of filling pressures in these patients with cardiomyopathy was undoubtedly secondary to the aggressive use of potent parenterally administered diuretic agents; all of these patients had previously presented to the hospital with pulmonary congestion and dyspnea.

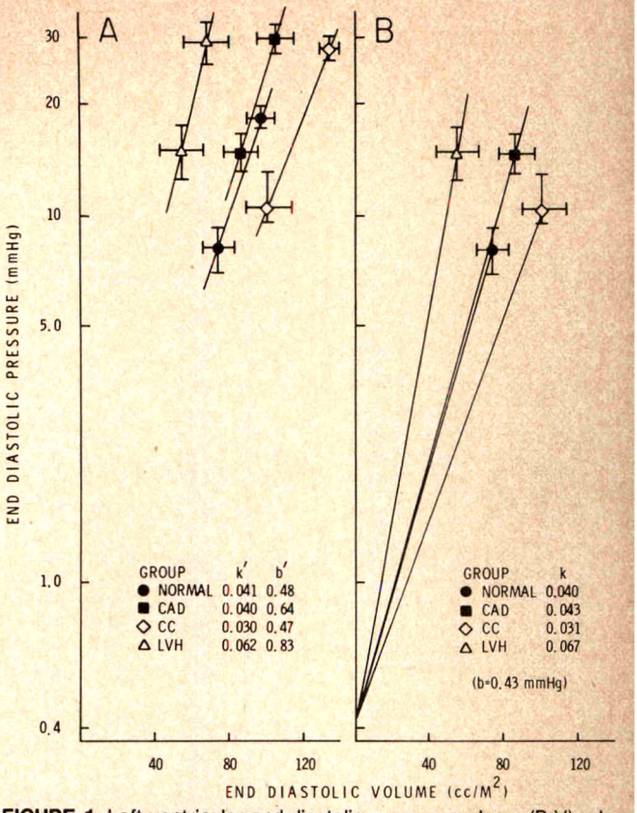

FIGURE 1. Left ventricular end-diastolic pressure-volume (P-V) relations in 22 patients. **A,** the average end-diastolic P-V coordinates (control period and angiotensin infusion) are plotted for each of the four groups. The slope (k′) of the ln P-V relation and the pressure intercept (b′) were determined from the two coordinates of P and V. **B,** the average end-diastolic P-V coordinates (control) are plotted; the slope (k) of the ln P-V relation was determined from a constant pressure intercept (b) of 0.43 mm Hg (animal data). CAD = coronary artery disease; CC = congestive cardiomyopathy; LVH = left ventricular hypertrophy.

After infusion of angiotensin, as described under Methods, a second coordinate of end-diastolic pressure and volume was obtained. The slope (k′) of the ln P-V relation obtained from two end-diastolic pressure-volume coordinates (control period and after angiotensin infusion) was calculated for each patient (Table I), and the average k′ for each group is represented graphically in Figure 1A by a line connecting the two coordinates. In the group with hypertrophy the ln P-V relation is to the left and k′ is greater than normal; in the group with cardiomyopathy, the ln P-V relation is to the right and k′ is less than normal. Although the average end-diastolic pressure of the group with coronary artery disease is significantly greater ($P < 0.02$) and the average end-diastolic volume is only slightly greater (P = not significant) than normal, the ln P-V slopes for these two groups are similar.

A pressure intercept (b′) at zero volume was obtained for each patient from the two coordinates of end-diastolic pressure and volume. The mean value of b′ for the groups with hypertrophy, coronary ar-

TABLE I

Clinical and Laboratory Data in 22 Patients

Case no.	Age (yr) & Sex	Diagnosis	BSA (m^2)	Heart Rate (beats/min)		LV Pressure (S/D/M) (mm Hg)		ED Volume (cc/m^2)		k'	b' (mm Hg)	k	(dV/VdP)-ed (10^{-2}/ mm Hg)	SEF (%)	SC (10^{-2}/ mm Hg)
				C	A	C	A	C	A						
Normal Heart															
1	49F	Normal	1.65	66	66	145/5/11	200/13/21	68	79	0.059	0.20	0.048	2.8	61	19
2	18M	Normal	1.81	100	85	130/4/6	150/12/16	52	78	0.038	0.84	0.051	6.3	62	32
3	22M	Normal	2.26	62	52	138/6/11	182/15/21	96	114	0.036	0.35	0.034	2.8	57	17
4	59M	Normal	1.65	91	69	115/2/5	155/10/19	70	102	0.043	0.27	0.035	8.2	59	29
5	21M	Normal	1.84	70	66	118/4/8	145/9/15	87	110	0.027	0.74	0.034	4.3	54	16
Average						/8.2	/18.4	75	97	0.041	0.48	0.040	4.9	59	23
± SEM						±1.2	±1.3	±8	±8	±0.005	±0.13	±0.004	±1.1	±2	±3.3
Coronary Artery Disease and Ventricular Asynergy															
6	67M	Anterior akinesia	1.97	92	84	145/8/15	182/18/26	112	133	0.026	0.80	0.032	1.9	25	2
7	63F	Inferior hypokinesia	1.43	96	78	132/6/9	160/8/15	48	59	0.046	0.97	0.063	3.7	48	13
8	49F	Anteroapical hypokinesia	1.64	94	85	105/6/11	145/18/34	120	158	0.030	0.31	0.027	2.8	21	4
9	51F	Anterior hypokinesia	1.69	68	64	140/8/17	157/15/30	80	98	0.032	1.36	0.046	1.6	44	6
10	48M	Inferior akinesia	2.05	80	80	110/4/8	165/25/38	63	92	0.054	0.27	0.046	4.3	42	10
11	50F	Anteroapical hypokinesia	1.87	84	90	165/15/20	190/19/31	76	86	0.044	0.72	0.051	1.3	30	4
12	44M	Apical akinesia	2.26	80	84	141/13/19	170/21/35	114	131	0.036	0.32	0.033	1.4	28	2
13	56M	Anterior hypokinesia	1.98	68	66	160/7/20	195/15/32	77	86	0.052	0.36	0.049	1.3	49	7
Average						/14.9	/30.1	86	105	0.040	0.64	0.043	2.3	36	6
± SEM						±1.8	±2.5	±9	±11	±0.004	±0.14	±0.004	±0.4	±4	±1.4
Congestive Cardiomyopathy															
14	62M	Cardiomyopathy	1.70	78	80	130/2/6	188/19/25	85	129	0.035	0.38	0.031	6.3	37	11
15	45M	Cardiomyopathy	1.74	100	104	145/5/8	182/15/23	92	135	0.025	0.84	0.032	4.3	29	5
16	41M	Cardiomyopathy	1.84	88	84	100/4/7	155/24/35	100	141	0.039	0.14	0.028	5.1	26	6
17	45M	Cardiomyopathy	2.32	93	90	120/6/12	153/18/28	93	119	0.024	0.58	0.036	2.5	29	4
18	53M	Cardiomyopathy	1.88	75	77	125/12/20	165/20/29	135	148	0.029	0.42	0.028	1.3	20	2
Average						/10.6	/28.0	101	134	0.030	0.47	0.031	3.9	28	5.6
± SEM						±2.6	±2.1	±13	±5	±0.003	±0.12	±0.002	±0.9	±3	±1.5
Left Ventricular Hypertrophy															
19	20F	Aortic stenosis	1.66	98	78	187/5/9	220/10/20	49	62	0.061	0.44	0.062	3.7	65	21
20	74M	Aortic stenosis	1.74	58	51	195/16/21	225/22/39	86	104	0.034	1.09	0.045	1.2	53	9
21	67F	IHSS	1.47	72	68	170/12/16	220/24/30	44	51	0.089	0.31	0.082	1.7	89	49
22	23M	IHSS	2.11	68	68	120/6/14	150/20/28	42	55	0.063	1.49	0.079	2.1	83	39
Average						/15	/29.3	55	68	0.062	0.83	0.067	2.2	73	29.5
± SEM						±2.5	±3.9	±11	±12	±0.011	±0.28	±0.009	±0.5	±8	±8.9

A = angiotensin infusion; b' (see k'); BSA = body surface area; C = control period; (dV/VdP)ed = end-diastolic compliance; ED = end-diastolic; IHSS = idiopathic hypertrophic subaortic stenosis; k = slope of the ln P-V relation (single coordinate method); k' = slope of the ln P-V relation and b' = pressure intercept (both were obtained from two coordinates of end-diastolic pressure and volume); SC = specific compliance; S/D/M = systolic/diastolic/mean; SEF = systolic ejection fraction.

TABLE II

Ventricular Function Data

Case no.	EDS (10^3 dynes/cm^2)	LMFS	PDS (10^3 dynes/cm^2)	Work Index (PDS × SV) (10^5 dyne-cm)
		Normal Heart		
1	32	29	352	144
2	17	37	355	114
3	43	34	351	193
4	16	43	314	129
5	28	42	319	150
		Congestive Cardiomyopathy		
14	19	45	328	101
15	30	42	398	107
16	25	45	296	77
17	43	40	332	90
18	63	29	380	103
		Idiopathic Hypertrophic Subaortic Stenosis		
21	28	22	239	93
22	24	23	166	58

EDS = end-diastolic stress; LMFS = linear muscle fiber stretch (see Methods); PDS = peak developed stress; SV = stroke volume.

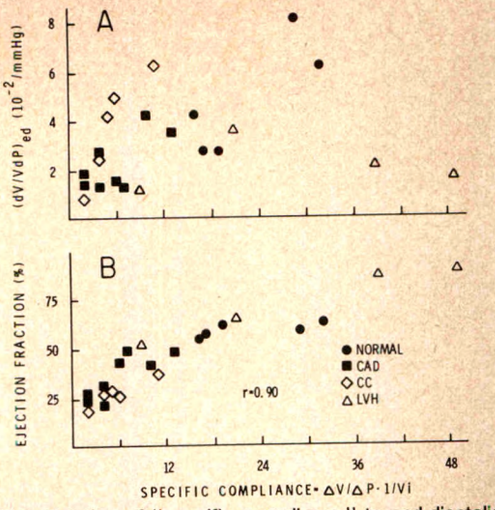

FIGURE 2. Relation of "specific compliance" to end-diastolic compliance [(dV/VdP)ed] and systolic ejection fraction. **A,** although there is agreement between (dV/VdP)ed and specific compliance in normal patients and those with coronary artery disease, discrepancies exist when patients with congestive cardiomyopathy and left ventricular hypertrophy are considered. **B,** specific compliance correlates well (r = 0.90) with the systolic ejection fraction.

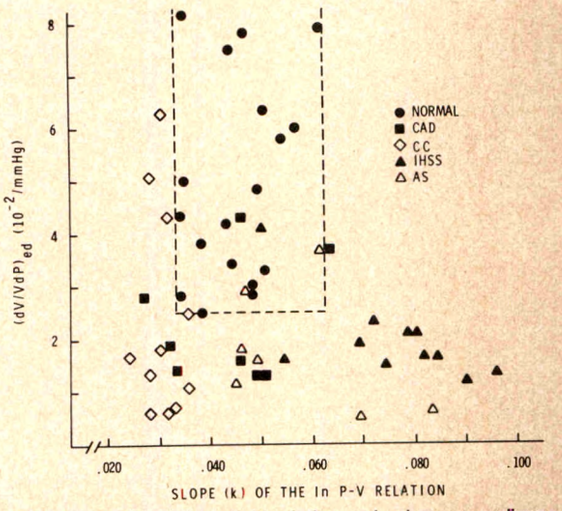

FIGURE 3. Slope (k) of the ln P-V relation and volume compliance at end-diastole in 55 patients. In congestive cardiomyopathy, the value for k is low but (dV/VdP)ed may be normal or depressed. In ventricular hypertrophy, k is high or normal but (dV/VdP)ed is generally reduced. In coronary artery disease, k varies widely, but (dV/VdP)ed tends to be depressed. The range of normal is outlined by the **broken line.** AS = aortic stenosis; IHSS = idiopathic hypertrophic subaortic stenosis.

tery disease, normal findings and cardiomyopathy was 0.83 ± 0.28, 0.64 ± 0.14, 0.48 ± 0.13, and 0.47 ± 0.12 mm Hg, respectively. The range for the entire group of 22 patients (0.14 to 1.49 mm Hg) was wide. Although the average b′ value tended to be higher in patients with a high k value and lower in patients with a low k value, the differences (in b′) between these groups were nonsignificant at the 0.05 level.

A value for the slope (k) of the ln P-V relation was calculated for each patient utilizing a single coordinate of end-diastolic pressure and volume (control) and a constant pressure intercept (b) of 0.43 mm Hg (Table I). The average value for k for each group is presented graphically in Figure 1B by a line between the average end-diastolic coordinate of pressure and volume, and b = 0.43 mm Hg. Again, the ln P-V relation is to the left in the group with hypertrophy, to the right in the group with cardiomyopathy and similar to normal in the group with coronary artery disease. When the slope was calculated from two coordinates, the result was similar to that obtained from a single coordinate of end-diastolic pressure and volume (see Fig. 1).

Left ventricular end-diastolic compliance: Since the values for the slope of the ln P-V relation were similar by the single and double coordinate methods, it follows that estimates of end-diastolic compliance would likewise be little changed if the simplified (single pressure-volume coordinate) method of obtaining (dV/VdP)ed were used in place of the multiple coordinate approach. In fact, the correlation between (dV/VdP)ed and (dV/VdP)ed′ was excellent (r = 0.90). For this reason, end-diastolic compliance and derived parameters are calculated and reported using the single coordinate method (Tables I and II, Fig. 2 to 4). This approach allows comparison among the average values for groups, but may be of limited value in the examination of individual patients.

The average end-diastolic compliance [(dV/VdP)ed] of the group with coronary artery disease ($2.3 \pm 0.4 \times 10^{-2}$ mm Hg^{-1}) was less ($P < 0.05$) than normal ($4.9 \pm 1.1 \times 10^{-2}$ mm Hg^{-1}). The value for this normal group is similar to that of a different

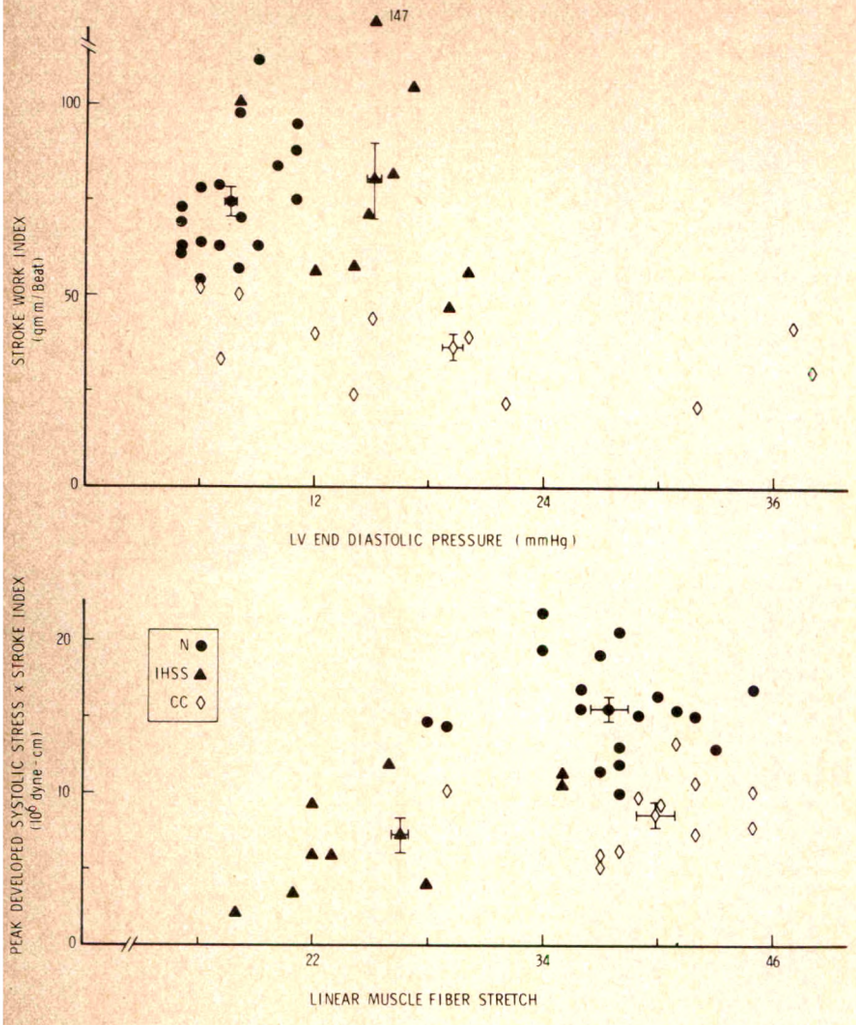

FIGURE 4. Left ventricular function curves. A conventional plot **(above)** of left ventricular stroke work against end-diastolic pressure suggests that systolic performance in idiopathic hypertrophic subaortic stenosis is achieved through increased end-diastolic fiber length; although performance is depressed in congestive cardiomyopathy, end-diastolic pressure varies widely. In contrast, when "linear muscle fiber stretch" is plotted against the product of peak developed systolic stress and stroke index (below), it appears that both systolic performance and fiber stretch are reduced in idiopathic hypertrophic subaortic stenosis; in congestive cardiomyopathy, systolic performance is reduced but fiber stretch is slightly greater than normal.

group of normal subjects previously described.[4] Compliance at end-diastole was less than normal ($P < 0.05$) in the group with hypertrophy ($2.2 \pm 0.5 \times 10^{-2}$ mm Hg^{-1}). Although the average end-diastolic compliance in the group with cardiomyopathy ($3.9 \pm 0.9 \times 10^{-2}$ mm Hg^{-1}) was lower than normal, the difference was nonsignificant at the 0.05 level.

Specific compliance ($\Delta V/\Delta P \cdot 1/V_i$): The average value for left ventricular specific compliance in the group with coronary artery disease ($6 \pm 1.4 \times 10^{-2}$ mm Hg^{-1}) was significantly lower ($P < 0.001$) than the average value for the normal group ($23 \pm 3.3 \times 10^{-2}$ mm Hg^{-1}). Specific compliance in the group with cardiomyopathy ($5.6 \pm 1.5 \times 10^{-2}$ mm Hg^{-1}) was likewise significantly less ($P < 0.01$) than normal, whereas the average value for the group with hypertrophy (29.5 ± 8.9) did not differ significantly from normal. The lowest values for specific compliance were obtained in patients with the hemodynamic findings of congestive cardiomyopathy and the highest values in patients with idiopathic hypertrophic subaortic stenosis. In Figure 2A (dV/VdP)ed is plotted against specific compliance. The value for specific compliance is very high and that for (dV/VdP)ed is low in patients with idiopathic hypertrophic subaortic stenosis, whereas patients with congestive cardiomyopathy have low values for specific compliance and low to normal values for (dV/VdP)ed. Thus, a positive correlation exists between these two methods of estimating diastolic compliance in normal subjects and those with coronary artery disease, but a lack of correlation is seen when patients with congestive cardiomyopathy and idiopathic hypertrophic subaortic stenosis are considered.

In Figure 2B, specific compliance is plotted against the systolic ejection fraction. A high correlation ($r = 0.90$) exists between these two variables; patients with cardiomyopathy had the lowest values for specific compliance and ejection fraction, whereas patients with idiopathic hypertrophic subaortic stenosis had the highest values for specific compliance and exhibited extreme degrees of systolic emptying. In contrast, there was no direct relation between (dV/VdP)ed and ejection fraction in any of the four groups studied.

Left ventricular function curves: To assess the active length-tension relations of these hearts, a work index (peak developed systolic stress × stroke vol-

ume index) of the left ventricle was plotted against end-diastolic linear muscle fiber stretch. The work index gives a ventricle credit for both force generation and fiber shortening, whereas fiber stretch is derived from end-diastolic stress and linear compliance corrected for wall thickness. This analysis was made for the patients in our study with a normal left ventricle, idiopathic hypertrophic subaortic stenosis or congestive cardiomyopathy (Table II); data from three groups of similar patients, previously described,[4] are combined with those from patients reported herein and left ventricular function curves are constructed in Figure 4. This analysis suggests that end-diastolic fiber stretch is reduced in idiopathic hypertrophic subaortic stenosis (average fiber stretch was 28 percent less than the average for the normal group), and that the reduced systolic performance seen in this group may be in part related to inefficient utilization of the Starling mechanism. Depressed systolic performance is apparent in the group with congestive cardiomyopathy; in this group, end-diastolic fiber stretch is slightly greater than normal (average fiber stretch was 8 percent greater than the average for the normal group). Conventional ventricular function curves (stroke work vs. end-diastolic pressure) are shown for comparison.

Discussion

Because several indexes have been used to define the diastolic properties of the left ventricle in man, it is important to define carefully the methods and assumptions in any clinical evaluation of ventricular compliance.[17] First, it should be reemphasized that the left ventricular diastolic stress-strain relation is nonlinear and that the exponential nature of the diastolic pressure-volume relation results in progressive reduction of end-diastolic compliance as the filling pressure increases. Thus, the level of end-diastolic compliance is abnormally low in any ventricle that is filled sufficiently. Second, the assumption regarding an exponential pressure-volume relation is made in this study only for end-diastolic pressure and volume and no attempt has been made to fit a simple exponential to data obtained throughout diastole. Restricting the analysis to end-diastole attenuates the effects of incomplete ventricular relaxation, which may be a major determinant of the diastolic pressure-volume relation especially in early diastole.[18] Importantly, since the Starling mechanism is adjusted at end-diastole, end-diastolic compliance (or resistance to stretch) becomes a critical determinant of end-diastolic fiber stretch and, thus, of systolic performance.

Diastolic Pressure-Volume Relations and Compliance

Pressure-volume relations: In this study the average slope (k′) of the ln P-V relation determined from *two* end-diastolic pressure-volume coordinates was similar to the average slope (k) determined from a *single* coordinate of end-diastolic pressure and volume and a pressure intercept (b) of 0.43 mm Hg. Evidence that the pressure intercept (b) varies little in the presence of reduced diastolic compliance (as in experimental myocardial infarction) has previously been reported,[4,19] and the pressure intercept has been found to be similar in patients with a normal left ventricle and in those with aortic stenosis.[4,20] By contrast, when changes in b were measured by Barry et al.[3] during pacing-induced angina pectoris, the value for b increased from an average of 1.05 mm Hg during the control period to an average of 2.25 mm Hg during angina. The range of b in our study was 0.14 to 1.49 mm Hg and, although the average b value for the group with cardiomyopathy was lower than the average for the group with hypertrophy, there was no consistent difference between patients with a large dilated heart and those with a small hypertrophic heart. Methodologic differences may be somewhat responsible for the variation in results, but acute changes in the diastolic properties of the left ventricle during angina must be considerably different from those observed during the chronic development of hypertrophy, dilation or scar formation. Since the average k values (and the average b values) for each group were similar by the single and double coordinate methods, we elected to utilize the simplified single coordinate approach to describe end-diastolic compliance and derived functions (linear compliance and muscle fiber stretch). In this study similarities and differences among groups are emphasized, but since k (and b) variability exist within groups, the single coordinate analysis may have limitations in the examination of individual patients. Accurate definition of diastolic pressure-volume or stress-strain relations await methods that employ frequent sampling of simultaneously measured pressure and volume.[10]

End-diastolic compliance: In agreement with previous reports,[1,4,14,21] end-diastolic compliance was found to be reduced in patients with left ventricular hypertrophy and in some with coronary artery disease. Since end-diastolic compliance may be reduced in ventricles that are smaller than normal (idiopathic hypertrophic subaortic stenosis), have a normal end-diastolic volume (coronary artery disease) or are larger than normal (congestive cardiomyopathy), it is proper to consider both k and (dV/VdP)ed in assessing the diastolic properties of diseased ventricles. The k value describes the overall relation between end-diastolic pressure and volume, whereas (dV/dP)ed and (dV/VdP)ed are determined by the operating pressure. Thus, a ventricle with a given value for k might be more or less compliant at end-diastole depending on the operating end-diastolic pressure. For these reasons, diuretic agents may reduce the operating pressure and thus increase end-diastolic distensibility or compliance, but k should not be affected. Likewise, a positive inotropic intervention, although not affecting the basic passive elastic properties of the muscle (no effect on k), could improve the systolic ejection fraction and thus reduce heart size; accordingly, end-diastolic compliance would increase.

In Figure 3, the relation between k and (dV/VdP)ed is illustrated for a total of 55 patients (the 22 patients in this study and 33 previously reported on[4]). In congestive cardiomyopathy, the value for k is low and (dV/VdP)ed ranges from low to normal; in hypertrophy, k is high or normal and (dV/VdP)ed is reduced; in coronary artery disease, k varies widely and (dV/VdP)ed is low. This analysis allows characterization of relative differences in pressure-volume relations as well as definition of compliance at end-diastole in ventricles with various types of disease.

Specific compliance: Some have attempted to define the diastolic pressure-volume relation and diastolic compliance by relating the total increase in diastolic volume (ΔV) to the increase in pressure that occurs throughout diastole (ΔP). Smith et al.[2,14] have calculated $\Delta V/\Delta P$ and have normalized this value for initial volume. Specific compliance ($\Delta V/\Delta P \cdot 1/V_i$) was calculated for each patient in our study and, although there was agreement between specific compliance and end-diastolic compliance [(dV/VdP)ed] in the normal subjects and those with coronary artery diseases, certain important discrepancies occurred when patients with congestive cardiomyopathy and idiopathic hypertrophic subaortic stenosis were considered (Fig. 2A). In idiopathic hypertrophic subaortic stenosis, the value for specific compliance was very high whereas that for end-diastolic compliance was very low; in cardiomyopathy, the value for specific compliance was low whereas that for end-diastolic compliance ranged from low to normal. The high values for specific compliance in idiopathic hypertrophic subaortic stenosis and reduced values in congestive cardiomyopathy parallel the values for systolic ejection fraction (Fig. 2B) and are at variance with general concepts of ventricular compliance in these two forms of heart disease. The good correlation between specific compliance and ejection fraction does not imply a causal relation between these two variables, but suggests that the former should be interpreted with caution in appraising certain clinical problems. For example, values for specific compliance have been found to be of some prognostic value in acute myocardial infarction,[2] but it is possible that this finding may be, in part, a reflection of the ejection fraction.

Left Ventricular Function Curves

An assessment of left ventricular active length-tension relations is provided by plotting the product of peak developed systolic stress and stroke volume (work index) against end-diastolic linear muscle fiber stretch (strain index). The concept of end-diastolic muscle fiber stretch is especially important because the ultrastructural basis of the Starling mechanism is not the absolute length of a muscle fiber but the degree to which the fiber is stretched. The work index utilized in this type of ventricular function curve credits the ventricle both for the development of force (stress) and for myocardial shortening. Figure 4 demonstrates that the normal ventricles and those with idiopathic hypertrophic subaortic stenosis define a work-length curve in which the patients differ in the degree of heterometric recruitment to determine systolic performance. In spite of normal preload, hearts with idiopathic hypertrophic subaortic stenosis recruit subnormal end-diastolic fiber stretch (and perform subnormally), which suggests that reduced compliance prevents efficient utilization of the Starling mechanism. Those with congestive cardiomyopathy operate on a depressed ventricular function curve with fiber stretch that is only slightly greater than normal.

Linear muscle fiber stretch: Despite markedly increased preload (end-diastolic stress), the average linear muscle fiber stretch in patients with congestive cardiomyopathy was only 8 percent greater than the average for the normal group. These data are consistent with the observations of Ross et al.,[22] who studied the effects of chronic dilatation on left ventricular end-diastolic sarcomere lengths; the average sarcomere length in these large dilated hearts was only 5 percent greater than normal. In contrast, the average muscle fiber stretch in idiopathic hypertrophic subaortic stenosis was 28 percent less than normal, in spite of normal preload. Sarcomere lengths are extremely variable in idiopathic hypertrophic subaortic stenosis, with both overstretched and short sarcomeres present within a given cell; large groups of sarcomeres measure less than 1.5 μ.[23] Decreased sarcomere lengths have also been demonstrated in right ventricular hypertrophy secondary to pulmonary arterial banding.[24] If the average end-diastolic sarcomere length in idiopathic hypertrophic subaortic stenosis is less than normal, then reduced systolic performance (Fig. 4) may be explained at least in part on this basis.

Clinical Implications

Many forms of heart disease produce symptoms more as a result of abnormal left ventricular diastolic compliance than of depressed contractility or reduced systolic performance. The most common symptom of idiopathic hypertrophic subaortic stenosis is said to be dyspnea,[25] whereas evidence for reduced systolic pump function is meager. Some patients with coronary artery disease may be restricted by symptoms of pulmonary congestion secondary to the "paradox of the stiff heart."[26] Symptoms in chronic constrictive pericarditis may be more related to abnormal ventricular compliance than to reduced cardiac contractility.[27] In contrast to these examples of fixed reduction in left ventricular compliance, transient abnormalities of volume compliance have been observed to occur during angina pectoris.[3,28] The importance of right ventricular distensibility as a determinant of the degree of intracardiac shunting in atrial septal defect is well known. The pattern of flow from the right ventricle to the pulmonary artery during ventricular diastole has been described in carcinoid heart disease and is said to be due to the combined effects of increased right atrial pressure, de-

creased right ventricular compliance and normal pulmonary arterial pressure.[29] The mechanisms and potential reversibility of these and other abnormalities of left ventricular compliance require further study. Although passive volume compliance of the left ventricle can be estimated by several methods, frequent sampling of simultaneously measured pressure and volume will be necessary to define optimally the continually changing relation between these variables during diastole.

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Hemodynamic Effect of Dobutamine in Patients with Severe Heart Failure

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Dobutamine, a derivative of dopamine, was infused at a rate of 10 μg/kg per min in 15 patients with severe congestive heart failure. Cardiac output increased from an average of 3.1 to 5.6 liters/min ($P < 0.001$) with no change in mean arterial pressure (93.3 to 98.2 mm Hg) and only a slight increase in heart rate (98.5 to 105.2 beats/min) ($P < 0.02$). Pulmonary wedge pressure was decreased from an average of 27.4 to 21.1 mm Hg ($P < 0.001$). In seven patients a dose of 5 μg/kg per min also produced a significant increase in cardiac output but the effect was less than with the 10 μg/kg per min dose. No side effects were observed during the infusion. Dobutamine therefore is a potent inotropic drug with limited chronotropic and peripheral vascular effects and deserves therapeutic trial in the short-term management of low output heart failure.

Although sympathomimetic amines are the most potent known agents for augmenting myocardial contractility, their clinical application for this purpose has been limited because of their chronotropic and peripheral vascular actions. Isoproterenol, for example, induces a marked increase in cardiac output but at the expense of a decrease in arterial diastolic pressure, tachycardia and increased myocardial irritability.[1–3] Norepinephrine, on the other hand, produces systemic vasoconstriction, which increases diastolic arterial pressure and thus may limit the increase in cardiac output and result in a reduction of regional perfusion.[4–6] Dopamine has been introduced as a sympathomimetic inotropic agent with less chronotropic and vasoconstrictive effect[7,8]; however, it has considerable vasoconstrictive properties in large doses, the cardiac output response is variable and arrhythmias have been reported.[9–11]

A derivative of dopamine, dobutamine ([±] -4-[2-] [3-(p-hydroxphenyl)-1-methyl propyl] amino] ethyl] pyrocatechol hydrochloride), has recently been synthesized by Tuttle and Mills[12] and has been demonstrated in early animal studies to have a relatively selective inotropic effect.[13] In this study we examined the acute hemodynamic response to dobutamine in patients with severe left ventricular failure. Our results indicate that this drug has potent cardiac stimulating properties with little effect on heart rate or blood pressure and therefore may prove to be a useful agent for the management of severe heart failure.

Methods

Studies were performed in 15 patients with severe chronic class III or class IV (New York Heart Association criteria) heart failure (primary myocardial, rheumatic or ischemic heart disease). Pertinent clinical data are summarized in Table I. All patients were male; their ages ranged from 39 to 76 (average 51) years. All were receiving maintenance doses of digitalis and had been treated with diuretic agents. The digitalis and diuretic agents were withheld for 24 hours before the study.

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TABLE I

Hemodynamic Effects of Dobutamine (10 μg/kg per min) in 15 Patients with Heart Failure

Case no.	Age (yr)	BSA	Diagnosis	State	MAP	HR	PAP	PCW	CO	SVR	PVR
1	48	1.86	CM	C	98	90	26	20	2.8	2800	229
				D	88	100	20	16	5.6	1257	57
2	45	1.52	CM	C	120	110	—	—	3.5	2743	—
				D	124	110	—	—	6.1	1574	—
3	41	1.84	CM	C	104	110	—	—	3.5	2377	—
				D	114	110	—	—	5.2	1753	—
4	50	1.78	RHD	C	70	96	17	12	2.9	1931	138
				D	80	108	15	10	3.8	1684	105
5	61	1.94	CM	C	80	90	25	18	3.3	1939	170
				D	90	96	19	13	4.7	1532	102
6	44	1.86	IHD	C	85	84	35	28	4.5	1511	124
				D	85	90	35	25	5.5	1236	145
7	46	2.18	CM	C	92	120	46	34	1.9	2918	497
				D	84	120	31	18	5.6	943	186
8	48	1.59	CM	C	84	100	43	34	2.1	2430	308
				D	93	96	38	28	4.1	1662	196
9	49	1.80	CM	C	112	120	43	34	4.0	1836	179
				D	114	120	40	28	4.6	1669	207
10	50	1.80	IHD	C	90	90	38	30	4.5	1372	142
				D	100	120	25	14	7.8	923	108
11	39	2.22	CM	C	118	94	40	22	3.1	2837	464
				D	117	94	34	14	4.7	1923	339
12	76	1.80	IHD	C	104	120	53	34	2.0	3390	737
				D	94	124	39	26	3.4	1929	305
13	63	1.64	CM	C	82	88	...	...	1.6	...	...
				D	86	92	...	...	5.8	...	...
14	49	2.10	CM	C	81	75	36	29	3.1	1820	189
				D	111	87	38	27	8.7	966	99
15	60	2.33	RHD	C	80	90	45	34	3.5	1826	251
				D	80	90	45	34	4.3	1488	204
Average (± SE)				C	93.3	98.5	37.3	27.4	3.1	2237	281
					±4.0	±3.7	±2.9	±2.0	±0.2	±157	±60
				D	98.2	105.2	31.6	21.1	5.6	1418	162
					±3.8	±3.3	±3.0	±2.1	±0.4	±112	±25
				P	NS	<0.02	<0.01	<0.001	<0.001	<0.001	<0.001

BSA = body surface area (m^2); C = control; CM = cardiomyopathy; CO = cardiac output (liters/min); D = dobutamine infusion; HR = heart rate (beats/min); IHD = ischemic heart disease; MAP = mean arterial pressure (mm Hg); NS = not significant; *P* = probability; PAP = mean pulmonary arterial pressure (mm Hg); PCW = pulmonary wedge pressure (mm Hg); PVR = pulmonary vascular resistance (dynes sec cm^{-5}); RHD = rheumatic heart disease; SE = standard error; SVR = systemic vascular resistance (dynes sec cm^{-5}).

Right heart catheterization was performed using a Swan-Ganz flow-directed balloon-tipped catheter inserted percutaneously by way of an antecubital vein. In 12 patients the pulmonary artery was successfully entered, but in 3 the catheter could not be advanced beyond the right atrium. The brachial artery was cannulated with a Teflon® needle. Arterial, pulmonary arterial and pulmonary capillary wedge (occluded) pressures were recorded using Statham P23 Db strain gauge transducers and a Hewlett-Packard recorder. Cardiac output in liters per minute was determined by the indicator-dilution technique using indocyanine green dye injected into the pulmonary artery and sampled from the brachial artery through a Gilford cuvette densitometer. Systemic vascular resistance in dynes sec cm^{-5} was calculated from the formula: (MAP − RAP) × 80/CO, where MAP is the mean arterial pressure in mm Hg, RAP is the mean right atrial pressure in mm Hg and CO is the cardiac output in liters/min. Pulmonary vascular resistance was calculated from the formula: (MPAP − PCW) × 80/CO, where MPAP is the mean pulmonary arterial pressure in mm Hg and PCW is the mean pulmonary capillary wedge pressure in mm Hg. Stroke work in g-m was calculated from the formula: (MAP − PCW) (SV) (0.0136) where SV is the stroke volume in ml.

After control hemodynamic measurements were obtained dobutamine (200 mg in 500 ml of dextrose in water) was administered intravenously as a continuous infusion at a rate of 10 μg/kg per min. In seven patients dobutamine was given at two dose levels, 5 and 10 μg/kg per min. Hemodynamic measurements were repeated after at least 15 minutes of constant infusion of the drug at each dose level.

Results

Hemodynamic data at rest and during infusion of 10 μg/kg per min of dobutamine in the 15 patients

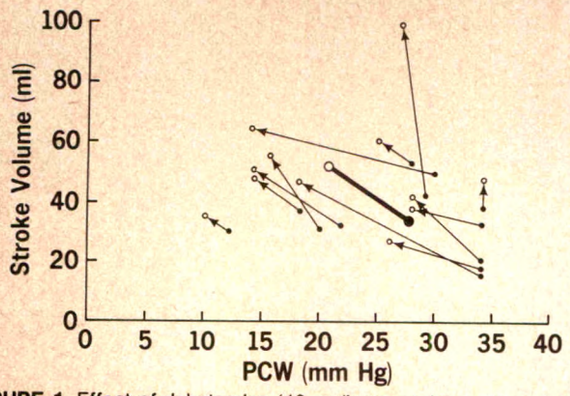

FIGURE 1. Effect of dobutamine (10 μg/kg per min) on the relation between stroke volume and pulmonary capillary wedge pressure (PCW). **Closed circles** represent control observations, **open circles** observations during dobutamine infusion. **Heavy line** represents the average values for all patients studied.

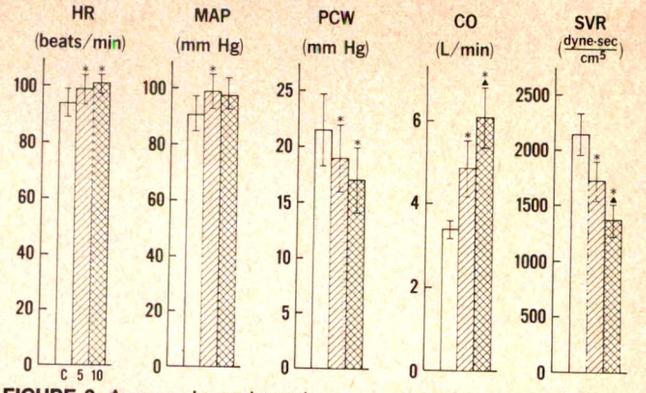

FIGURE 2. Average hemodynamic measurements in seven patients during control period **(open bar)** and infusions of 5 μg/kg per min **(middle bar)** and 10 μg/kg per min of dobutamine **(right bar).** Asterisk indicates significant difference from control ($P < 0.05$); triangle indicates significant difference from values during 5 μg/kg per min infusion ($P < 0.05$). CO = cardiac output; HR = heart rate; L = liters; MAP = mean arterial pressure; PCW = pulmonary wedge pressure; SVR = systemic vascular resistance.

studied are shown in Table I. Cardiac output increased in every patient ($P < 0.001$), from an average of 3.1 to 5.6 liters/min (81.8 percent), whereas heart rate changed only slightly (average 98.5 to 105.2 beats/min, $P < 0.02$), indicating that the increase in cardiac output was due mainly to the alteration in stroke volume, which increased by an average of 65.8 percent. The cardiac index was less than 2.5 liters/min per m^2 in all subjects during the control period and was restored to the normal range in 10 (67 percent) of the patients during dobutamine infusion. Mean pulmonary capillary wedge pressure in 12 patients decreased from 27.4 to 21.1 mm Hg during infusion of the drug ($P < 0.001$) (Fig. 1).

Mean arterial pressure was not significantly altered (93.3 to 98.2 mm Hg) during infusion of dobutamine, but systolic pressure increased from an average of 120 ± 5.5 (standard error) to 136 ± 5.5 mm Hg ($P < 0.05$) whereas diastolic pressure was unaltered (79 ± 3.5 to 82 ± 3.2 mm Hg). Cardiac work almost doubled as indicated by an increase in mean stroke work from 28.3 to 57.5 g-m ($P < 0.01$). The values for both systemic and pulmonary vascular resistance decreased during the drug infusion, from an average of 2,237 to 1,418 dynes sec cm^{-5} ($P < 0.001$) and from 281 to 162 dynes sec cm^{-5} ($P < 0.001$), respectively.

The 10 μg/kg per min infusion produced a greater hemodynamic effect than the 5 μg/kg per min infusion in the seven patients who were studied at both dose levels (Fig. 2). No arrhythmias or untoward side effects were observed in any patients during dobutamine infusion.

Discussion

Our data indicate that dobutamine possesses pharmacologic properties that make it an ideal sympathomimetic agent for producing a selective improvement in myocardial function. In the doses employed in these patients with severe congestive heart failure, cardiac output was restored to normal levels, pulmonary capillary wedge pressure was reduced, heart rate was only slightly increased whereas mean arterial pressure was unchanged.

Since myocardial oxygen consumption is directly related to aortic pressure and heart rate as well as to the contractile state of the myocardium,[14] sympathomimetic amines that increase heart rate (isoproterenol) or systemic vascular resistance (norepinephrine) may have a deleterious effect on the ischemic left ventricle.[3,15,16] Use of dobutamine in this clinical setting may be advantageous because this drug does not have prominent chronotropic or peripheral vascular effects but retains a potent inotropic effect. The reduction in peripheral vascular resistance during dobutamine infusion is consistent with either a direct vasodilating effect of the drug or a reflex relaxation of vascular tone.

Clinical implications: The incremental circulatory effect demonstrated when the dose was increased from 5 to 10 μg/kg per min indicates that within this dose range the hemodynamic response is linearly related to dose. Because of the prompt response to the drug, its reliability in restoring cardiac output to normal levels and the absence of side effects during these short-term infusions, further evaluation of the use of dobutamine in the treatment of low output syndromes is indicated. Since most of the patients in our series were less than 50 years old and had cardiomyopathy, additional data are needed on the responses in older patients with ischemic heart disease.

Acknowledgment

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Effects of Isosorbide Dinitrate on the Response to Atrial Pacing in Coronary Heart Disease

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To study the efficacy of isosorbide dinitrate in prevention of myocardial ischemia, 20 patients with angiographically proved coronary artery disease underwent atrial pacing (mean rate 138/min) before (P_1), 10 minutes after (P_2) and 65 minutes after (P_3) sublingual administration of 5 mg of isosorbide dinitrate. The symptomatic, hemodynamic and metabolic responses were evaluated at rest and during each pacing period. Angina occurred in all subjects during P_1. Angina did not recur or was less severe in 17 of 19 patients during P_2 and in 19 of 20 patients during P_3. Resting left ventricular end-diastolic pressure for the group was normal at 11 ± 4 mm Hg (mean ± standard deviation). On interruption of pacing at 4.5 minutes during P_1, average end-diastolic pressure during sinus rhythm was abnormal (18 ± 6 mm Hg). After administration of isosorbide dinitrate mean left ventricular end-diastolic pressure was significantly decreased at rest and remained normal when pacing was interrupted during P_2 and P_3. Brachial arterial pressure, cardiac index, tension-time index, left ventricular stroke work index and maximal rate of rise of left ventricular pressure were all diminished at rest before and during P_2 and P_3. S-T segment depression was less during P_2 and P_3 than during P_1. Before isosorbide dinitrate was given, resting myocardial lactate extraction was 15 ± 11 percent; during P_1 lactate extraction decreased to −2 ± 25 percent. Lactate extraction was significantly greater during P_2 and P_3 than during P_1.

This study demonstrates that sublingual administration of 5 mg of isosorbide dinitrate has a significant protective effect against pacing-induced myocardial ischemia at 10 and 65 minutes after administration.

Isosorbide dinitrate is one of the most widely used of the so-called long-acting nitrates in the management of angina pectoris. It has been given both orally and sublingually, either alone or in combination with propranolol.[1–3] Although most reports have suggested that it achieves better control of angina when administered sublingually, others have claimed that excellent prophylaxis can be achieved by administering daily oral doses of up to 360 mg.[4] Most studies show isosorbide dinitrate is beneficial, although some have found it to be no more effective than placebo.[5]

Both the mechanism and the duration of action of isosorbide dinitrate are unknown. The drug probably acts through alterations in the balance between myocardial oxygen demand and supply by decreasing left ventricular oxygen requirements. It may also change total coronary blood flow and distribution, but there have been no definitive studies of its effect on the coronary circulation. Investigations into the drug's duration of action have shown beneficial effects on hemodynamics and exercise tolerance ranging from less than 1 to at least 2 hours.[6–10] The different exercise protocols employed may account in part for the variable results reported in these studies.[11]

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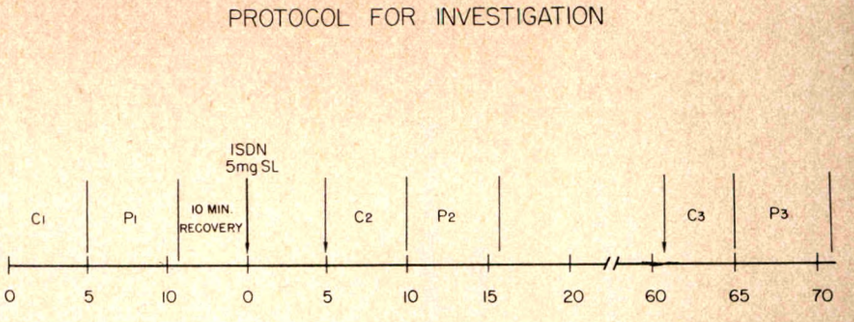

FIGURE 1. Protocol for sequential pacing studies. C_1, C_2, C_3 = first, second and third control periods before, 5 minutes after and 60 minutes, respectively, after drug administration; ISDN = isosorbide dinitrate; P_1, P_2, P_3 indicate, respectively, pacing periods before and 10 and 65 minutes after drug administration.

Previous investigations of the antianginal effects of isosorbide dinitrate have determined the response to exercise before and after drug administration.[1–3,5–10] Atrial pacing is well documented as a valid and reproducible stress test in patients with coronary artery disease and has been utilized to study the effect of nitroglycerin on the clinical, hemodynamic and metabolic concomitants of myocardial ischemia.[12–15] However, no information is available regarding the effect of sublingually administered isosorbide dinitrate on the response to atrial pacing in patients with symptomatic coronary artery disease. Accordingly, this study examines the early and late clinical, hemodynamic and metabolic effects of sublingually administered isosorbide dinitrate using atrial pacing as a stress.

Methods

Twenty patients with angina pectoris who were subsequently shown to have significant coronary artery disease were studied. Each patient was a potential candidate for saphenous vein coronary bypass surgery. Informed consent was obtained and there were no complications related to the investigation. Sodium Nembutal® (100 mg) was given orally 1 hour before the procedure. A single electrocardiographic lead (modified lead II) was monitored to evaluate S-T segment depression. Under local anesthesia, the brachial artery and two veins were isolated in the right antecubital fossa. A no. 8 Gorlin catheter was positioned in the mid-portion of the coronary sinus for pacing and blood sampling, a no. 8 Goodale-Lubin catheter was advanced to the pulmonary artery and a no. 8 Eppendorf catheter was passed to the left ventricle from the right brachial artery. With use of the Seldinger technique, a Teflon® cannula was inserted into the left brachial artery for blood sampling and arterial pressure monitoring. Pressures from the brachial artery, pulmonary artery and left ventricle were measured with P_{23}DB Statham strain gauges 5 cm below the angle of Louis and were recorded on a photographic recorder (Electronics for Medicine DR12). Mean brachial arterial and pulmonary arterial pressures and maximal systolic rate of rise of left ventricular pressure (dP/dt) were obtained electronically. Each measurement was averaged over at least two respiratory cycles.

Protocol (Fig. 1)

Control pressures and cardiac output determinations in duplicate were obtained by the dye-dilution technique. Blood samples were obtained simultaneously from the coronary sinus and brachial artery for subsequent analysis of lactate concentration (C_1). Each patient then underwent pacing from the coronary sinus at a rate of 120 to 150 beats/min (P_1). The rate was preselected with the aim of inducing angina within 3 to 4 minutes of the onset of pacing. Pacing was continued for 7 minutes with three 15 second periods of interruption at 1, 3 and 4.5 minutes, respectively, to measure left ventricular end-diastolic pressure during sinus rhythm. Cardiac output was determined and blood samples were taken between 5 and 7 minutes of pacing. After a 10 minute recovery period, 5 mg of isosorbide dinitrate was given sublingually. After 5 minutes (C_2) and 60 minutes (C_3), during sinus rhythm, pressures and cardiac output were recorded and blood samples obtained. After C_2 and C_3, pacing was repeated at the same rate for each patient starting at 10 minutes (P_2) and 65 minutes (P_3) after administration of isosorbide dinitrate. During P_2 and P_3 hemodynamic and metabolic data were obtained as during P_1.

After the hemodynamic study, selective coronary arteriography with use of the Sones technique and left ventriculography were performed. All patients had significant obstructive coronary disease with 75 percent or greater obstruction in at least one major coronary artery.

Calculations

Left ventricular end-diastolic pressure was measured at the nadir of the atrial deflection (*A*) in the left ventricular pressure tracing. In the tracings in which the *A* wave could not be clearly defined, end-diastolic pressure was measured at a point corresponding to the peak of the R wave of the electrocardiogram or where an abrupt rise in the pressure curve was visible.

Tension-time index (TTI) in millimeters of mercury × 10^{-1} was calculated according to the formula TTI = BA systolic × HR × 10^{-1} where BA = brachial arterial pressure in millimeters of mercury and HR = heart rate in beats per minute. Left ventricular stroke work index (LVSWI) in gram-meters per square meter was calculated according to the formula: LVSWI = [SI × (BAm − LVEDP) × 13.6]/1000 where SI = stroke index in milliliters per square meter, BAm = mean brachial arterial pressure in millimeters of mercury and LVEDP = left ventricular end-diastolic pressure in millimeters of mercury.

Blood samples for determination of lactate concentration were collected in glass tubes with no additive and immediately spun and frozen at −5° C for later analysis. Lactate concentration, determined by the automated enzymatic method of Apstein et al.,[16] was expressed as milligrams per 100 ml of plasma and the percentage of myocardial extraction of lactate was calculated as the ratio of the arteriovenous difference to the arterial level (a-v/a) × 100.

Statistical analyses were performed using Student's paired *t* test.

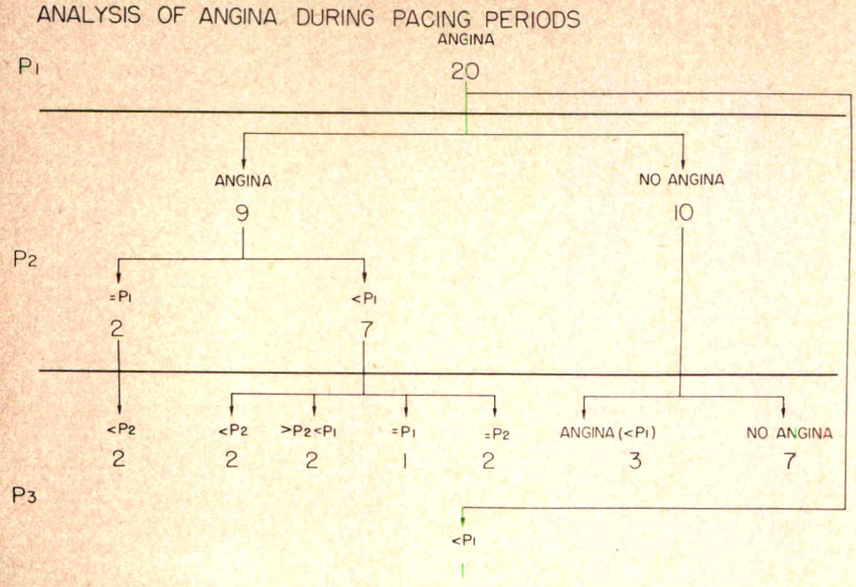

FIGURE 2. Analysis of angina during pacing periods. Abbreviations as in Figure 1.

Results

Angina during pacing: Figure 2 shows an analysis of the occurrence of chest pain during the three pacing periods. Angina developed in each of the 20 patients during the first pacing period (P_1). During P_2 (10 minutes after drug administration) only nine patients had angina; the pain was less severe than during P_1 in seven patients and equally severe in two. P_3 (65 minutes after drug administration) produced angina in 13 patients that was less severe than that during P_1 in all but 1 patient. The patient who did not undergo pacing during P_2 had less severe angina during P_3 than during P_1. Thus, angina did not recur or was less marked in 17 of 19 patients during P_2 and in 19 of 20 patients during P_3.

Hemodynamics during pacing: The hemodynamic and metabolic data are summarized in Table I, and statistical comparisons are shown in Table II. At the 4.5 minute interruptions of pacing and during the immediate post-pacing periods, heart rate returned to control values. The heart rate during sinus rhythm was similar during each control period. Left ventricular end-diastolic pressure was abnormal (more than 12 mm Hg) in six patients during the initial control period (C_1), but the average value was normal. During the initial pacing period (P_1) left ventricular end-diastolic pressure decreased from 11 ± 4 (mean ± standard deviation) to 8 ± 4 mm Hg ($P < 0.015$). During interruption of pacing at 4.5 minutes left ventricular end-diastolic pressure was 15 mm Hg or more in 14 patients and averaged 18 ± 6 mm Hg. This was a significant increase from the value obtained during C_1 ($P < 0.001$). These hemodynamic observations are commonly documented during myocardial ischemia induced by atrial pacing.[12–14] During all subsequent pacing and at periods of interruption the average left ventricular end-diastolic pressure remained normal. During the early pacing period after isosorbide dinitrate administration (P_2), none of the patients had abnormal end-diastolic pressure during interruption of pacing although nine had chest pain. During P_3 end-diastolic pressure on interruption was abnormal in only three of the patients who experienced angina and the mean value was normal (10 ± 4 mm Hg).

Cardiac index averaged 3.3 ± 0.5 liters/min per m^2 during C_1 and fell significantly 5 minutes (C_2) and 60 minutes (C_3) after drug administration ($P < 0.001$). Cardiac index during both P_2 and P_3 was significantly lower than during P_1.

Mean brachial arterial pressure did not change significantly 5 minutes after drug administration (C_2), but the decrease at 60 minutes (C_3) was significant ($P < 0.001$). There was a significant increase in brachial arterial pressure during P_1 but not during P_2 and P_3. The level of brachial arterial pressure during P_2 and P_3 was significantly lower than during the initial pacing period. Changes in tension-time index paralleled those of brachial arterial pressure.

Left ventricular stroke work index decreased after administration of isosorbide dinitrate from 54 ± 10 g-m/m^2 during C_1 to 44 ± 10 during C_2 and 37 ± 7 during C_3 ($P < 0.001$). During P_1 stroke work index decreased significantly as a result of the increased heart rate and hence decreased stroke index; the values during P_2 and P_3 were still lower than during P_1 ($P < 0.001$). During each pacing period left ventricular dP/dt increased. After administration of isosorbide dinitrate dP/dt decreased during both C_2 ($P < 0.015$) and C_3 ($P < 0.005$) and was also significantly reduced during pacing.

S-T segment depression was measured only during sinus rhythm because of the distortion introduced by coronary sinus pacing. During the control periods before and after drug administration S-T segments were isoelectric. After interruption of pacing before administration of isosorbide dinitrate the average S-T segment depression was 1.3 mm; after administration of isosorbide dinitrate it was significantly less during the two periods of pacing ($P < 0.001$).

TABLE I

Hemodynamic and Metabolic Data*

	HR (beats/min)	LVEDP (mm Hg)	LVEDP (INT) (mm Hg)	CI (liters/ min per m²)	BAm (mm Hg)	TTI (mm Hg/min × 10^{-1})	LVSWI (g-m/beat per m²)	dP/dt (mm Hg/sec)	S-T (mm)	Lactate Extraction (%)
C_1	80 ± 14	11 ± 4	. . .	3.3 ± 0.5	101 ± 15	1119 ± 294	54 ± 10	1536 ± 428	0	15 ± 11
P_1	138 ± 11	8 ± 4	18 ± 6	3.4 ± 0.5	111 ± 13	1942 ± 409	35 ± 6	1850 ± 490	−1.3	−2 ± 25
C_2	82 ± 13	7 ± 3	. . .	2.8 ± 0.5	99 ± 13	1105 ± 278	44 ± 10	1465 ± 390	0	12 ± 13
P_2	138 ± 11	5 ± 4	6 ± 3	2.7 ± 0.5	94 ± 13	1613 ± 231	24 ± 6	1725 ± 412	−0.5	10 ± 13
C_3	79 ± 14	8 ± 3	. . .	2.7 ± 0.5	86 ± 13	922 ± 248	37 ± 7	1296 ± 342	0	13 ± 9
P_3	138 ± 11	5 ± 3	10 ± 4	3.1 ± 0.6	93 ± 18	1598 ± 371	27 ± 7	1631 ± 362	−0.4	9 ± 15

*All values are mean ± standard deviation.

BAm = mean brachial arterial pressure; C_1, C_2, C_3 = first, second and third control periods before, 5 and 60 minutes after, respectively, drug administration; CI = cardiac index; dP/dt = maximal systolic rate of rise of left ventricular pressure; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVEDP (INT) = left ventricular end-diastolic pressure during interruption after 4.5 minutes of pacing; LVSWI = left ventricular stroke work index; P_1, P_2, P_3 = first, second and third pacing periods before, 10 and 65 minutes after, respectively, drug administration, S-T = S-T segment depression; TTI = tension-time index.

TABLE II

Summary of Significance of Changes (*P* Values)

	C_1-C_2	C_1-C_3	P_1-P_2	P_1-P_3	C_1-INT_1	INT_1-INT_2	INT_1-INT_3
HR	NS	NS	NS	NS	NS	NS	NS
LVEDP	<0.001	<0.01	NS	NS	<0.001	<0.001	<0.001
CI	<0.001	<0.001	<0.001	<0.02	. . .	. . .	. . .
BAm	NS	<0.001	<0.001	<0.001	. . .	. . .	. . .
TTI	NS	<0.001	<0.001	<0.001	. . .	. . .	. . .
LVSWI	<0.001	<0.001	<0.001	<0.001	. . .	. . .	. . .
dP/dt	<0.015	<0.005	<0.025	<0.015	. . .	. . .	. . .
S-T segments	. . .	. . .	. . .	. . .	<0.001	<0.001	<0.001
% lactate extraction	NS	NS	<0.02	<0.03	. . .	. . .	. . .

INT_1, INT_2, INT_3 = interruptions of pacing at 4.5 minutes of P_1, P_2 and P_3, respectively; NS = not significant; other abbreviations as in Table I.

Metabolic data: Lactate extraction averaged 15 percent during C_1. During P_1 there was a shift to lactate production for the group as a whole that averaged 2 percent. Among the 17 patients in whom metabolic sampling was performed lactate production occurred in 8. In the other nine patients the coronary sinus concentration tended to increase, resulting in a smaller arteriovenous difference. During C_2 three patients continued to show evidence of lactate production but for the group as a whole lactate extraction averaged 12 percent. During P_2 only four patients produced lactate; for the group, lactate extraction averaged 10 percent. During C_3 no patients showed evidence of lactate production. During P_3 five patients showed evidence of lactate production; for the group, lactate extraction averaged 9 percent.

Discussion

We have shown that administration of 5 mg of isosorbide dinitrate sublingually exerts a protective effect on the response to atrial pacing in patients with coronary artery disease. The subjective response of each patient with regard to lessening of chest pain is supported by objective hemodynamic and metabolic data showing an effect lasting at least 70 minutes in the majority of patients. Similar conclusions regarding the long-term effects of isosorbide dinitrate on hemodynamics at rest and during exercise have been reached by other investigators.[7–9]

During bicycle or treadmill exercise, angina occurs at a relatively constant level of myocardial oxygen consumption for each patient.[11] Changes in the determinants of myocardial oxygen consumption and the amount and duration of exercise at which angina occurs can be used to evaluate the efficacy of antianginal drugs. However, differences in exercise protocols employed may affect the ability to detect changes in exercise performance.[11] Use of right atrial pacing to precipitate angina provides an easily standardized, reproducible stress that is particularly suitable in the assessment of response to drug therapy.

Isosorbide dinitrate and myocardial oxygen consumption: The major determinants of myocardial oxygen consumption are left ventricular wall tension, heart rate and inotropic state.[17] Wall tension varies directly with chamber diameter and developed pressure and inversely with wall thickness. If one assumes that the decrease in left ventricular end-diastolic pressure after administration of isosorbide dinitrate at rest or during pacing is due to a decrease in left ventricular size, then part of the beneficial action

of this drug would be explained. We did not measure chamber size directly, but, in one study of the effects of isosorbide dinitrate total heart size did diminish on plain chest films after administration of the drug.[6] Systemic arterial blood pressure was significantly reduced during sinus rhythm and atrial pacing for at least 1 hour after administration of isosorbide dinitrate. This reduction would result in reduced left ventricular wall tension and, hence, reduced myocardial oxygen consumption. We did not assess contractile state, but it has been shown in animal studies that isosorbide dinitrate exerts a positive inotropic effect on isolated papillary muscle preparations which, in turn, would increase myocardial oxygen consumption.[18] The beneficial effects of isosorbide dinitrate on myocardial ischemia observed in our patients imply that the drug's actions on reducing myocardial oxygen consumption predominate. The role of changes in the coronary circulation induced by isosorbide dinitrate, which might also lead to a more favorable balance between myocardial oxygen supply and demand, is unknown.

Left ventricular end-diastolic pressure: Increase in left ventricular end-diastolic pressure on interruption of atrial pacing has been established as the hallmark of an ischemic response.[14] The relative importance of an increase in heart size or diminished left ventricular compliance during ischemia as determinants of this response is still being debated.[19–22] Whatever the cause, the increase in end-diastolic pressure on interruption of pacing was considerably less even 1 hour after isosorbide dinitrate was administered. An unexpected finding was the normalization of the end-diastolic pressure response to pacing even in patients who experienced angina during the second and third pacing periods. Previous investigations[12–14] have shown that pacing-induced angina is usually accompanied by an abnormal hemodynamic response. Apparently isosorbide dinitrate reduced heart size and, hence, left ventricular end-diastolic pressure in these patients, but this effect was not always sufficient to prevent myocardial ischemia during pacing.

Lactate metabolism: The metabolic data in this study also provide objective confirmation that isosorbide dinitrate exerts a beneficial effect on myocardial ischemia for as long as 70 minutes after its administration. Myocardial ischemia causes a shift from aerobic to anaerobic metabolism with lactate production.[23,24] Previous investigations[25] have shown that atrial pacing is a sensitive method for assessing lactate production by ischemic myocardium because there is no change in arterial lactate concentration as there is with exercise. When the arterial lactate level is constant, changes in coronary sinus lactate concentration are an accurate reflection of the metabolic state of the myocardium. Although individual variations in lactate metabolism were wide, the group as a whole tended to produce lactate during the first pacing period. At 15 and 70 minutes after administration of isosorbide dinitrate, metabolic status was improved, as shown by a return to lactate extraction.

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USV VASO-QUIZ NO.1

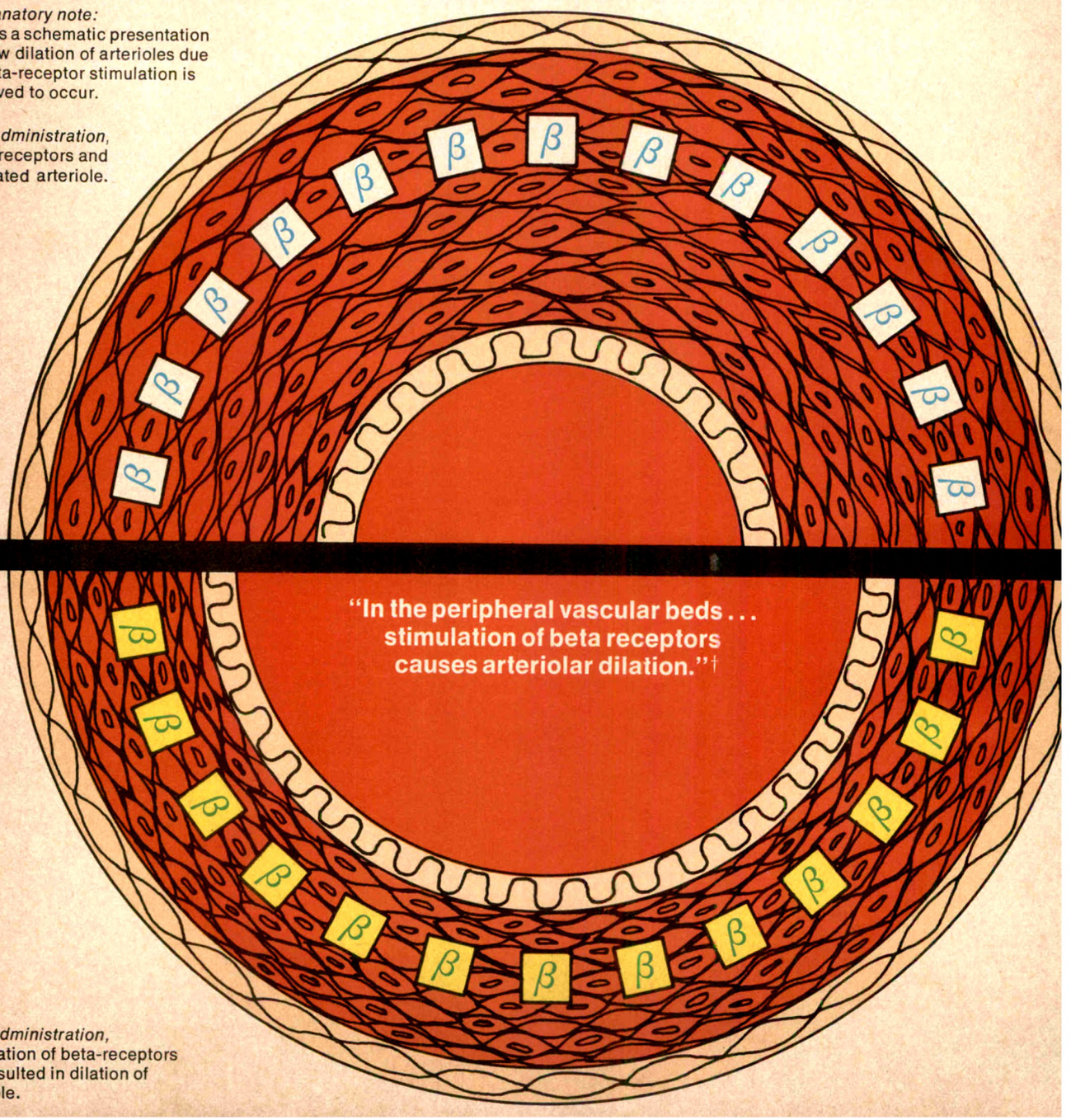
What chronic vascular disorder do these photos and symptoms describe?

1. Characteristic symptoms due do malnourishment of the skin may include atrophic changes, scaly appearance and dryness. Hair is sparse on toes and dorsa of the feet.

2. Impaired blood supply leads to characteristic nail changes: irregular growth, changes in shape and form and—commonly observed—slow growth.

Explanatory note:
This is a schematic presentation of how dilation of arterioles due to beta-receptor stimulation is believed to occur.

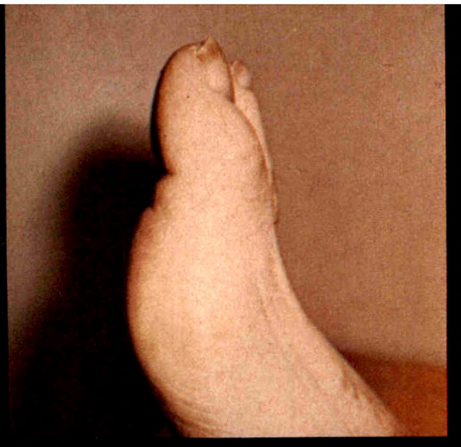
Pre-administration,
beta-receptors and undilated arteriole.



"In the peripheral vascular beds . . . stimulation of beta receptors causes arteriolar dilation."†

Post-administration,
stimulation of beta-receptors has resulted in dilation of arteriole.

Dependent rubor (a cyanotic redness) usually more intense in distal parts of e extremities, most often distal to wrists nd ank



4. Pallor of the skin on elevation of the affected extremities is caused by impaired circulation inadequate to overcome the effect of gravity.

Answer: Arteriosclerosis obliterans. These early changes suggest the need for instituting peripheral vasodilation therapy.

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STIMULATES BETA-RECEPTORS

DILATES ARTERIOLES IN SKELETAL MUSCLES

- to help increase blood supply to ischemic areas*
- to help relieve leg cramps, tingling, numbness, cold hands and feet*

*ndications**

- arteriosclerosis obliterans
- thromboangiitis obliterans (Buerger's disease)
- diabetic vascular disease
- night leg cramps
- ischemic ulcer
- Raynaud's phenomenon and disease

Miller, R.R. et al.: The pharmacologic basis for clinical use of beta-adrenergic blocking drugs, lation. Drug Ther. 8:2, April 1974.

ARLIDIN® (nylidrin HCl)

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 500.

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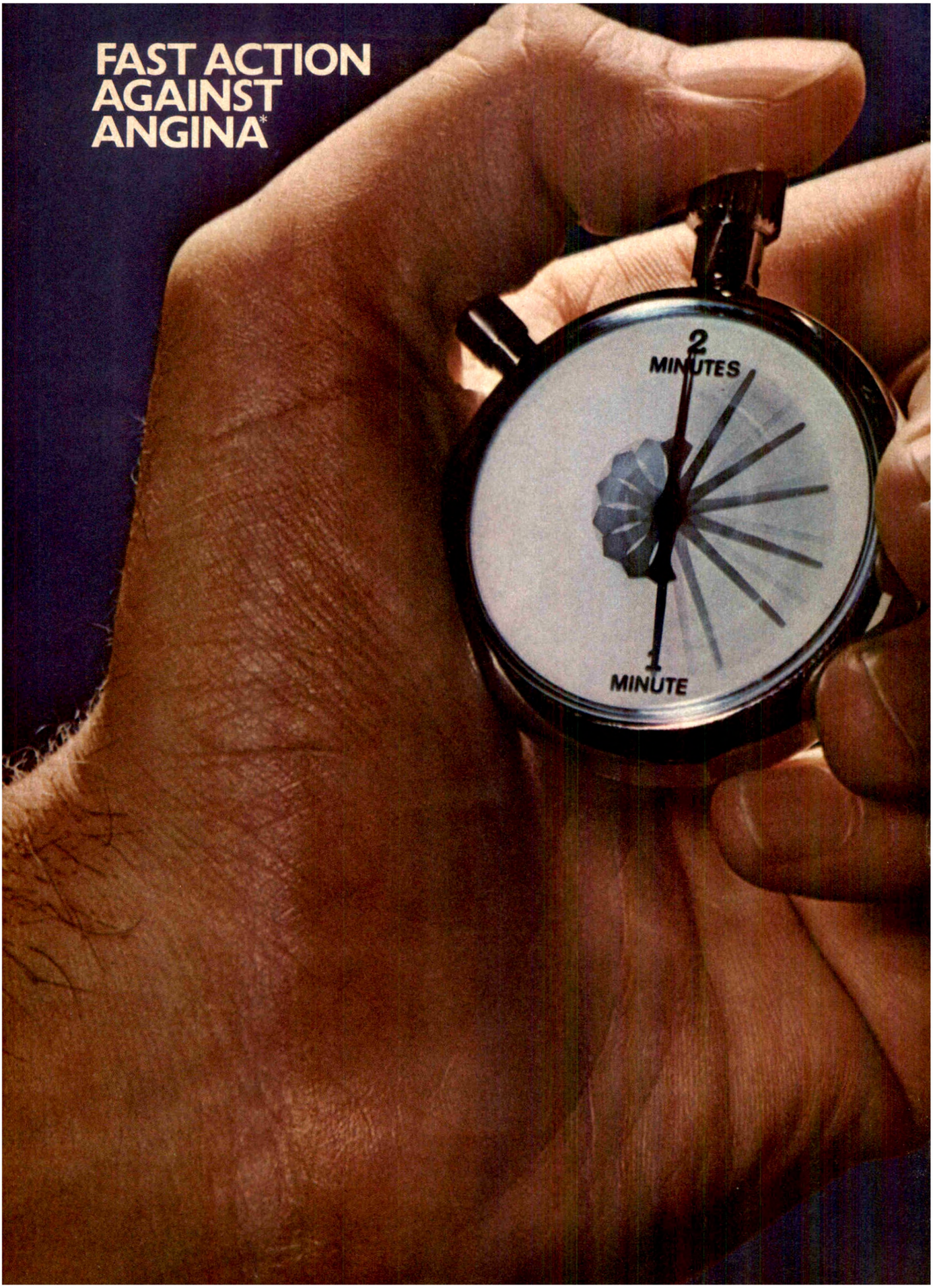
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SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

* **Indications:** Based on a review of this drug by The National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE.

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS
Division of ICI United States Inc.
Wilmington, Delaware 19897

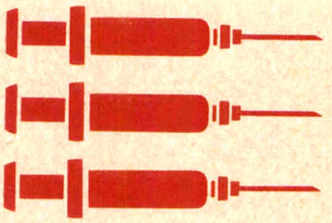
Effectiveness...

I.V. Administration Guidelines for Premature Ventricular Contractions and Tachycardia

1. Preparation of drug: Dilute before I.V. use.
2. Usual dosage range: 200-1000 mg.
3. Infusion rate: Not to exceed 25-50 mg. per minute. Total I.V. dose not to exceed 1000 mg.
4. Precautionary measures:
   a. Keep patient in supine position.
   b. Monitor electrocardiographically and discontinue if myocardial toxicity is evidenced.
   c. Measure blood pressure almost continuously and temporarily discontinue infusion if blood pressure falls more than 15 mm. Hg.

When therapeutic blood levels are required quickly, I.V. Injections

100 mg. every 5 minutes until arrhythmia suppressed (up to a maximum dose of 1 gram).



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2-6 mg. per minute[1].
(42.8 μg./min./kg.)[2]

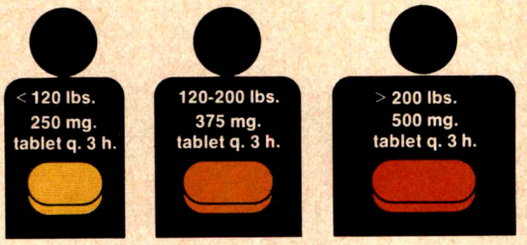
1. Wyman MG, Hammersmith L: Am J Cardiol 33:661-667, 1974
2. Bigger JT, Jr., Giardina EV: MCV Quart 9 (1): 65-76, 1973

Terminate I.V. infusion *4 hours before* oral regimen begun.

Oral Administration Guidelines to Provide 50 mg./kg./day* for Ventricular Arrhythmias

Ventricular Tachycardia
(give priming dose of 1 g. if patient has not received prior infusion)

Premature Ventricular Contractions



*This dosage schedule is for use as a guide for treating the average patient, but all patients must be considered on an individual basis.

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(Procainamide Hydrochloride)
through the entire therapeutic course

See next page for brief summary.

PRONESTYL® TABLETS
(Procainamide Hydrochloride Tablets)

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

Pronestyl Tablets (Procainamide Hydrochloride Tablets) are veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

Administration: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

How Supplied: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100.

PRONESTYL® INJECTION
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Description: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is a sterile aqueous solution providing 100 mg. or 500 mg. procainamide hydrochloride per ml. The 100 mg./ml. potency contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives. The 500 mg./ml. potency contains 0.1% methylparaben and not more than 0.2% sodium bisulfite as preservatives.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

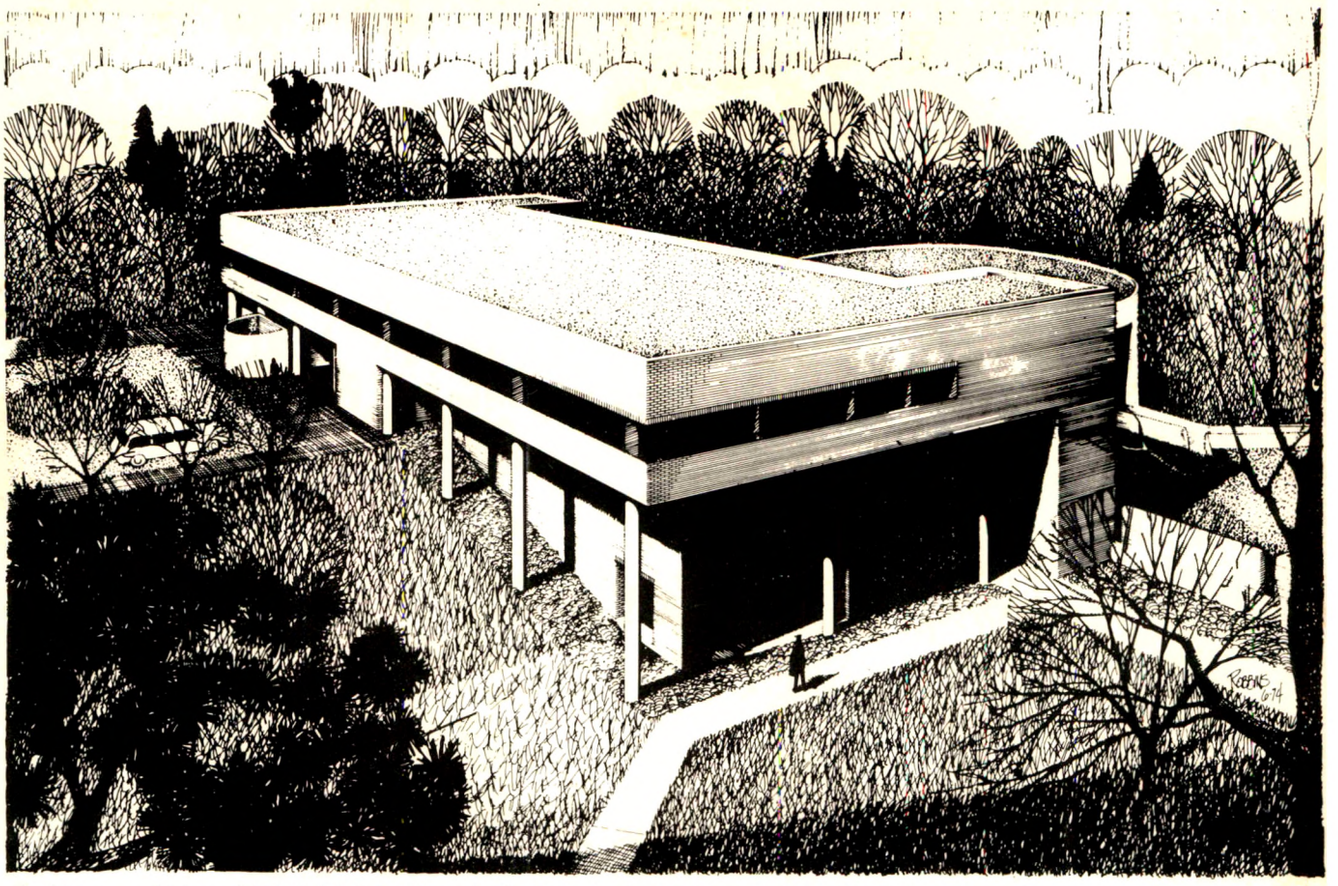
A syndrome resembling lupus erythematosus has been reported. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. *Intravenous use should be limited to extreme emergencies,* **the drug should be administered as a dilute infusion,** and the patient should be monitored electrocardiographically. The intravenous dose should not exceed 1 gram. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions.

How Supplied: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is available in 10 ml. vials providing 100 mg./ml. and in 2 ml. vials providing 500 mg./ml. © 1974 E. R. SQUIBB & SONS, INC. 444-009



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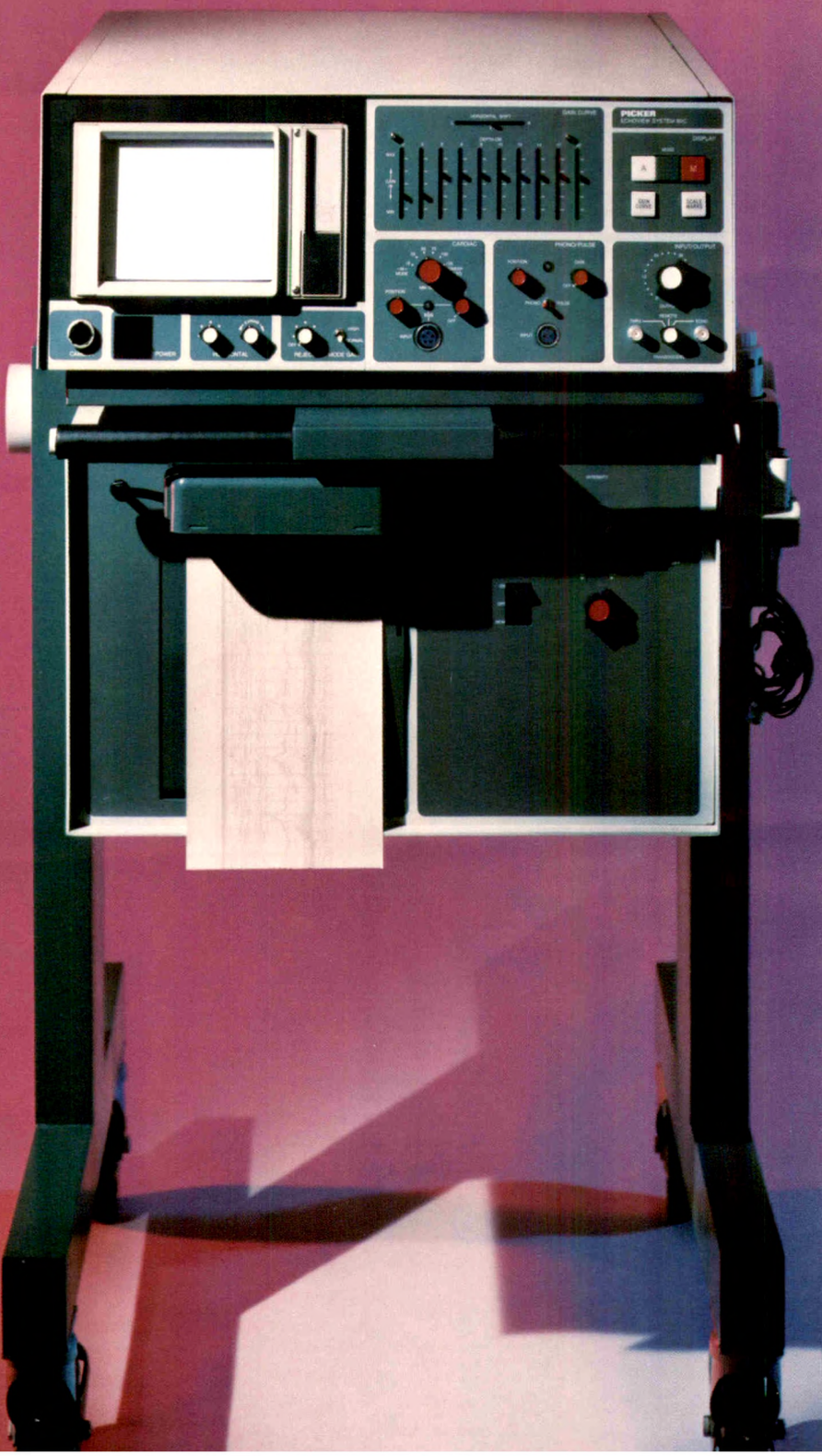

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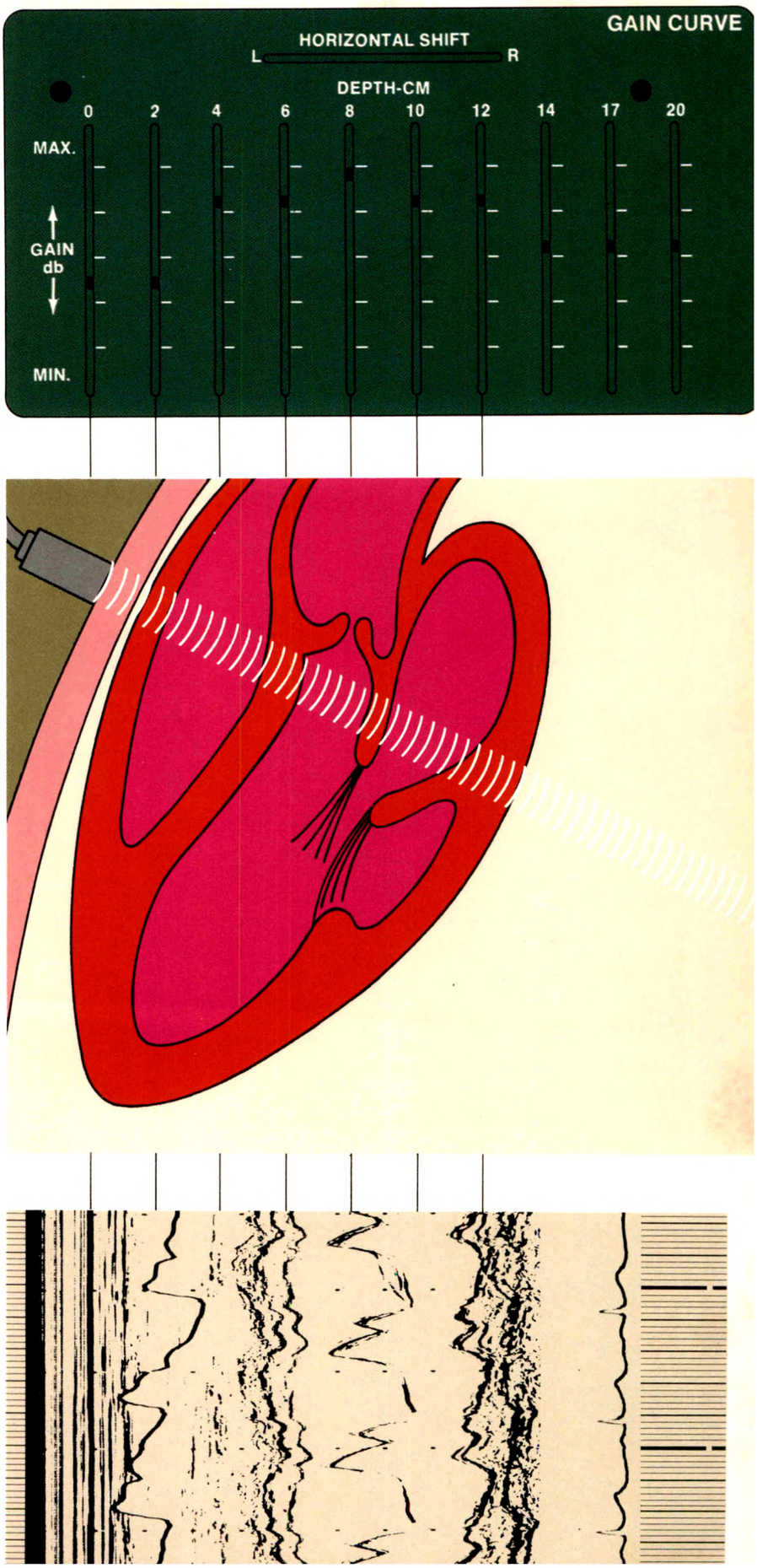

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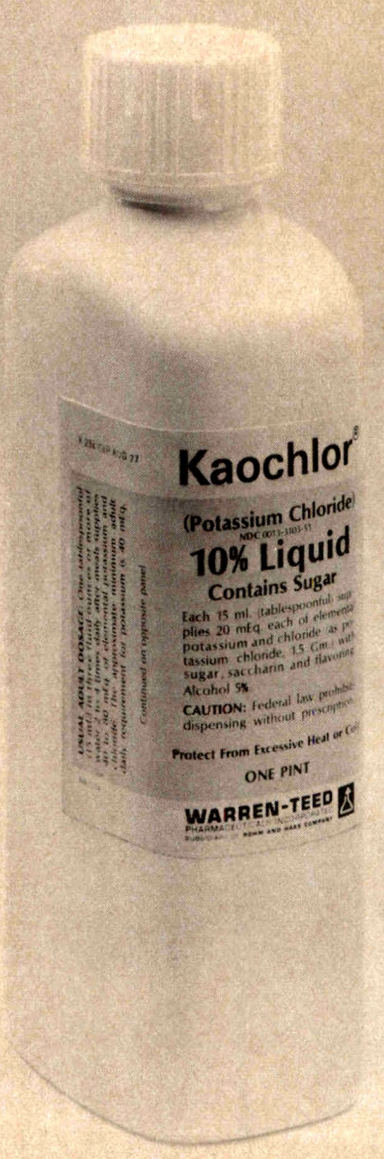

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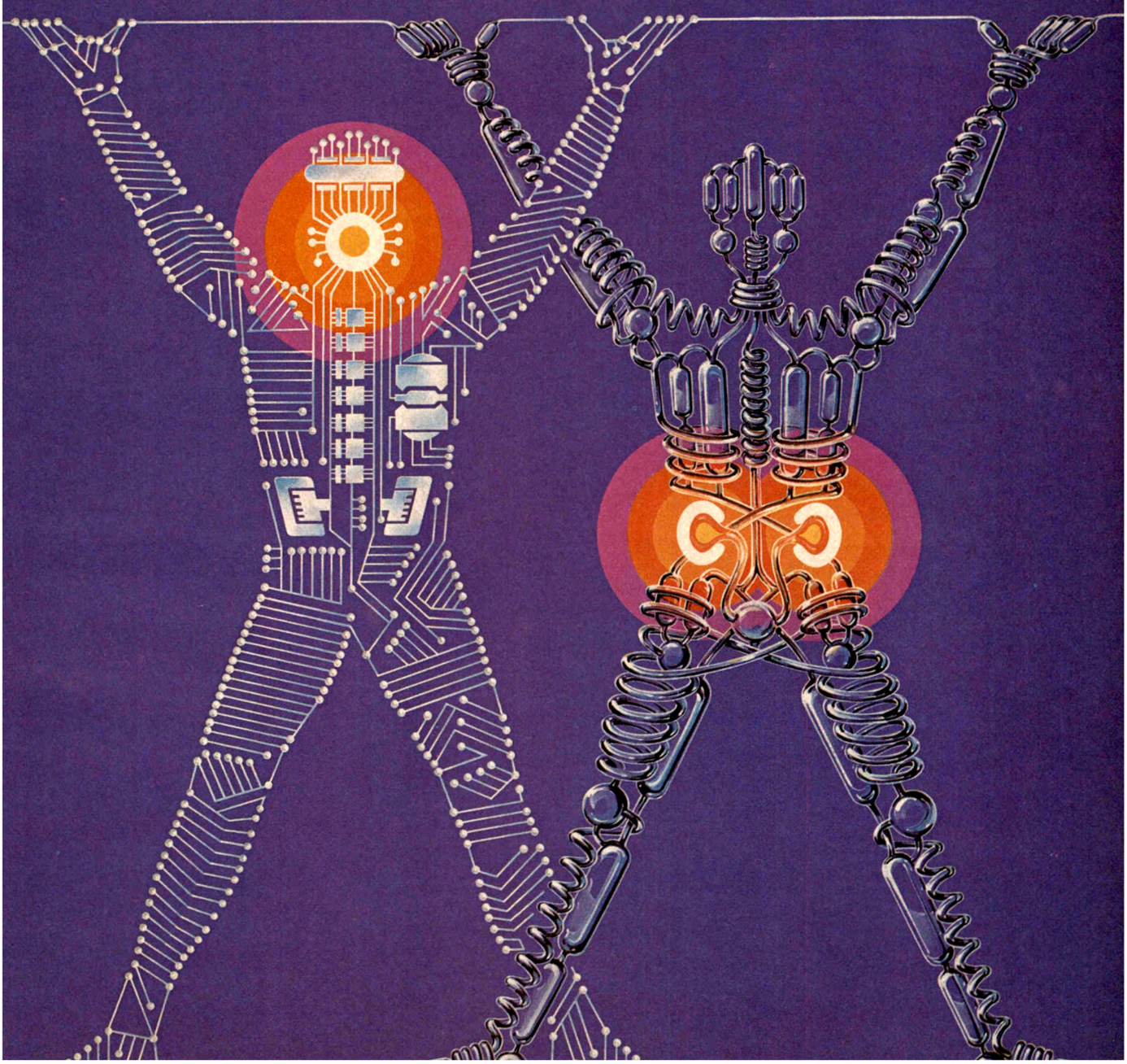

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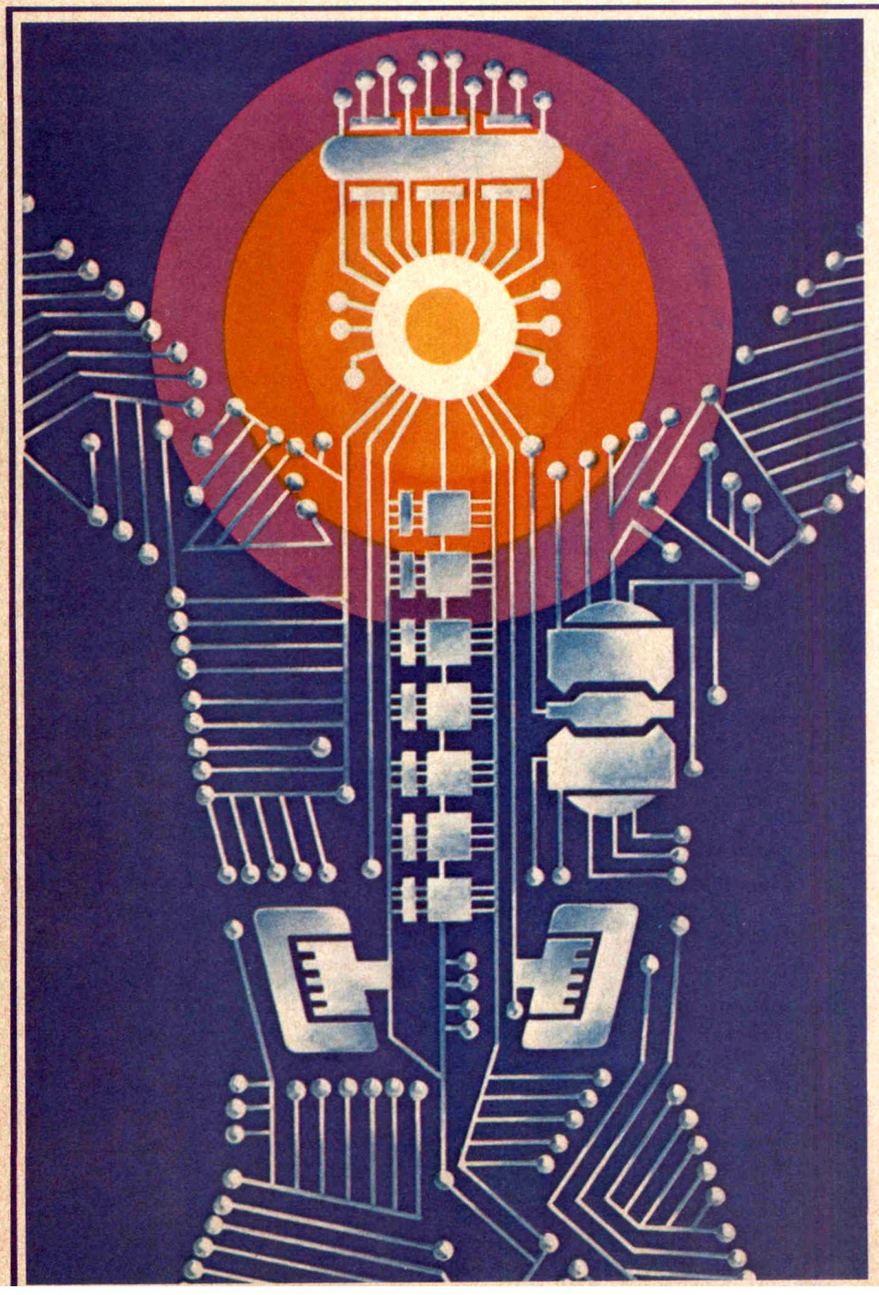

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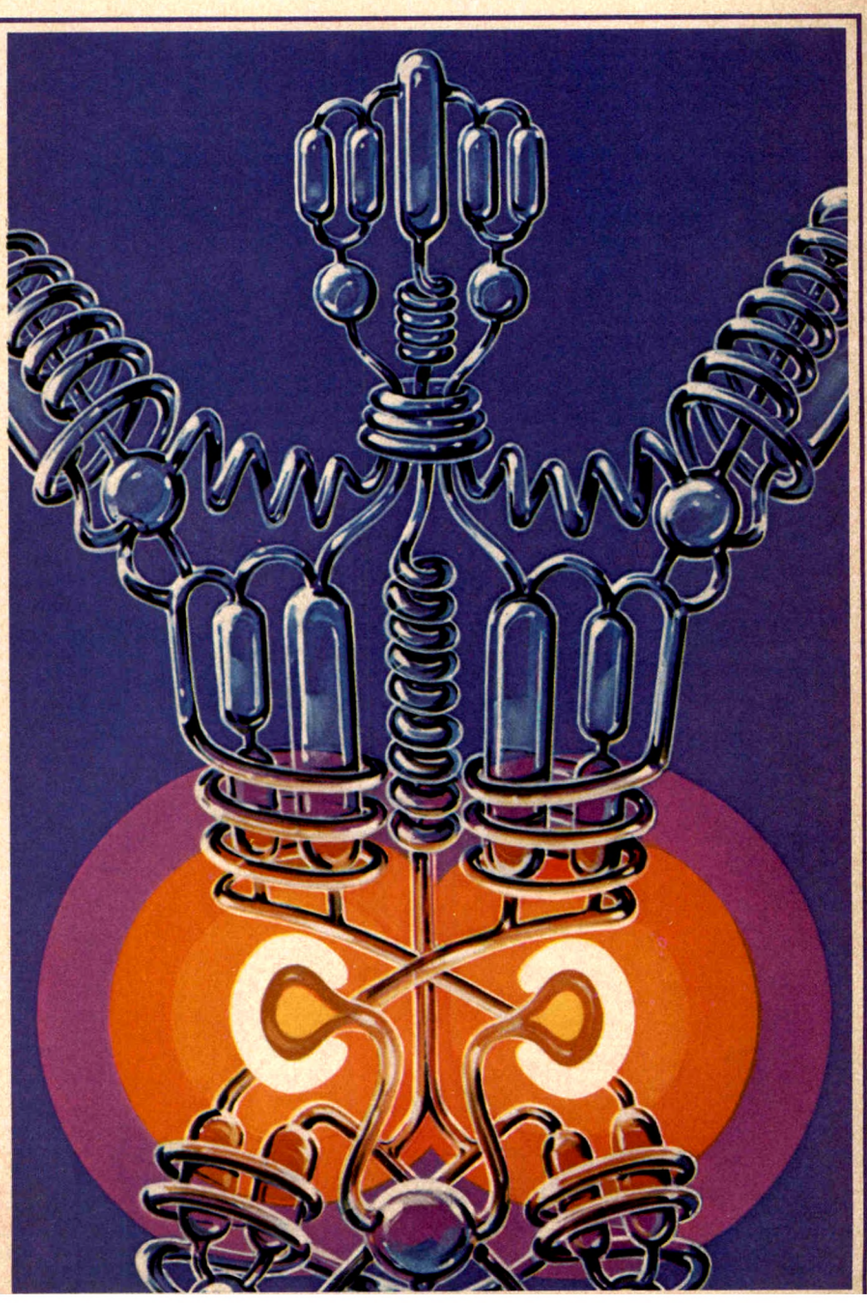

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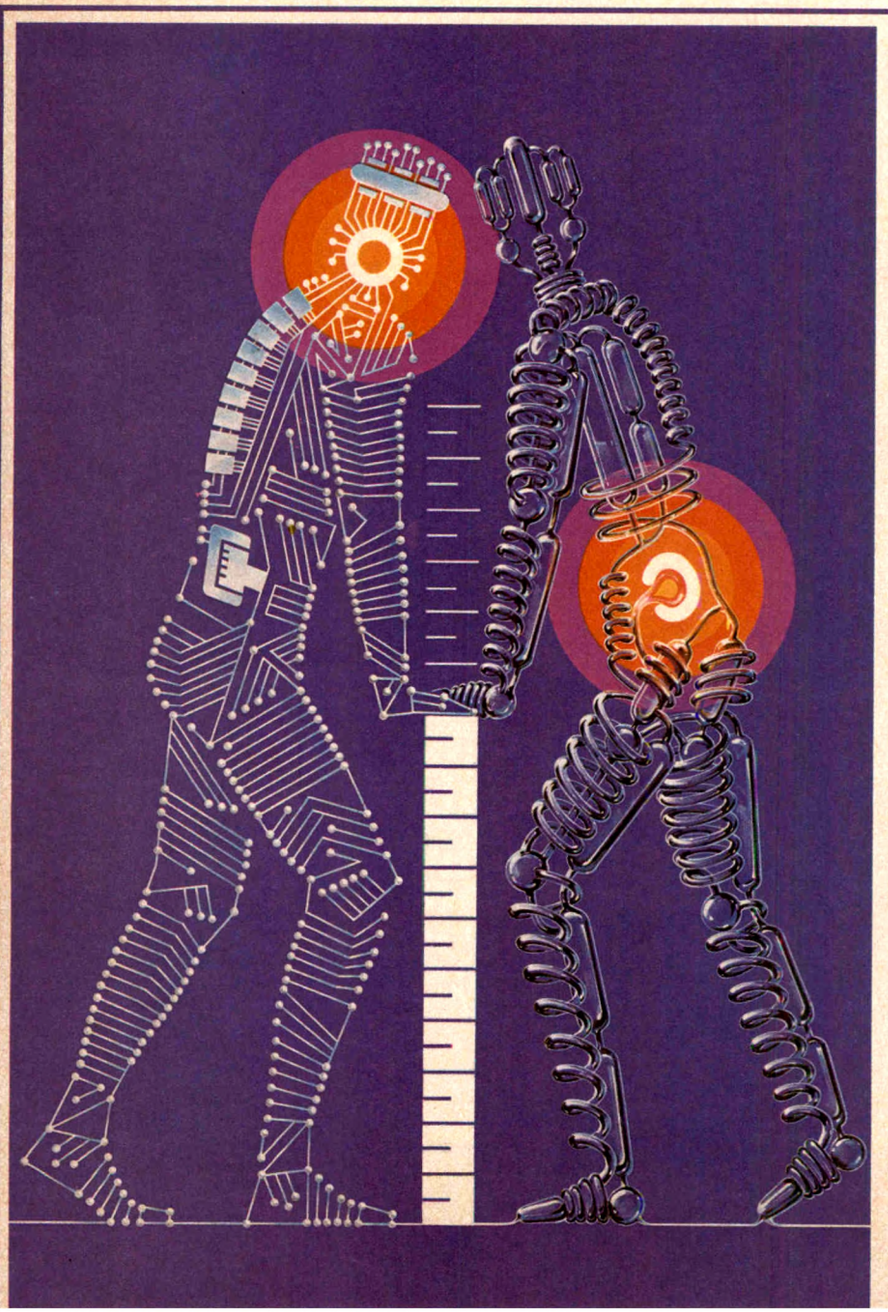

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Convenience and economy encourage patients to stay on medication, help assure continued blood pressure control over the long course of therapy*

*__WARNING__ Combipres is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

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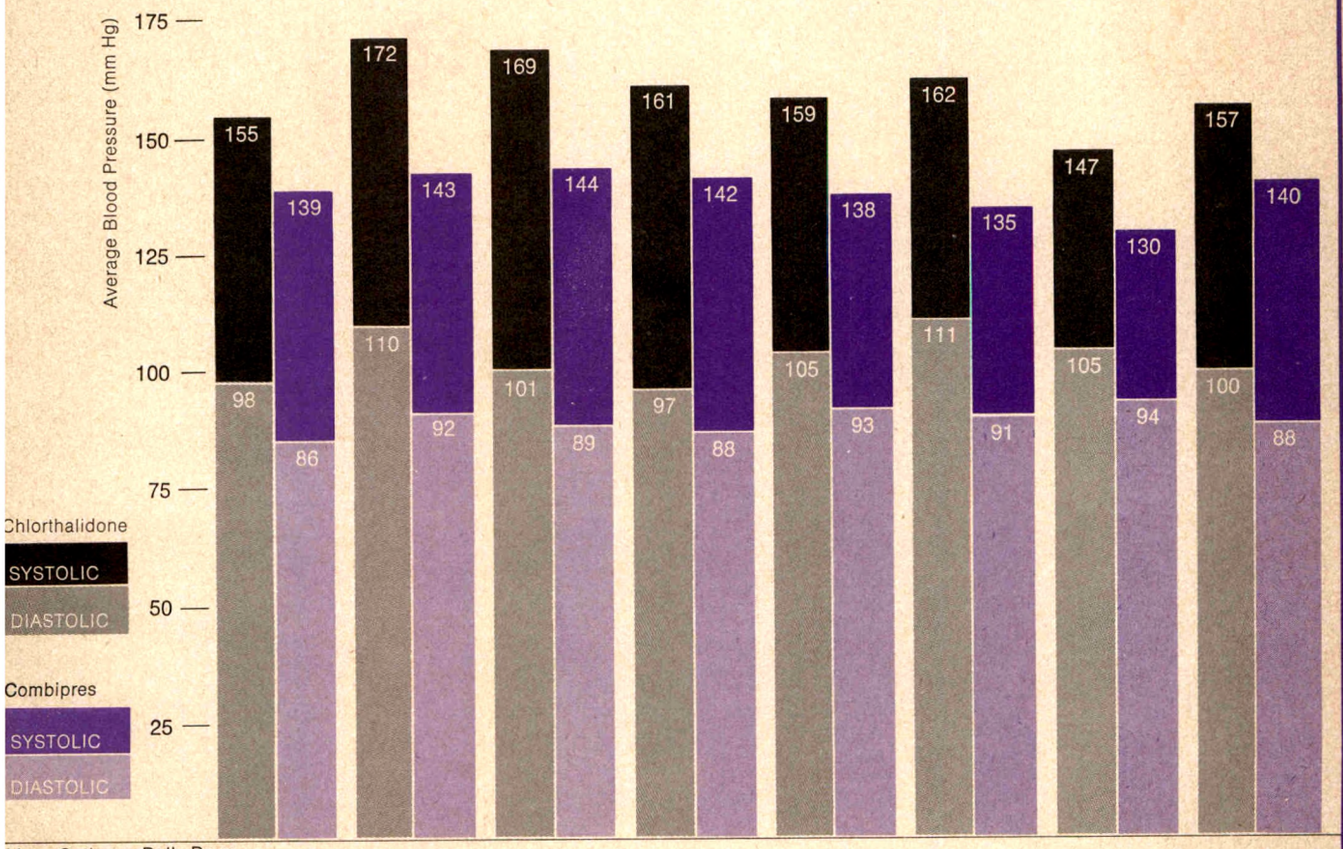

Mean Optimum Daily Dose Chlorthalidone (mg)	50	50	47.7	50	50	50	71	50
Combipres (mg)	0.3	0.48	0.47	0.4	0.43	0.68	0.52	0.4
No. of Patients who completed study	42	20	11	17	34	9	31	9
Study	1	2	3	4	5	6	7	8

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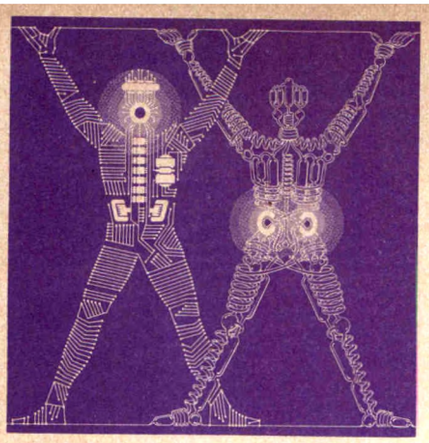

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Guidelines for Titrating Catapres and Chlorthalidone Dosages:

Initial doses: Catapres—one 0.1 mg tablet twice daily. Chlorthalidone—50 mg daily.

Dosage increments: While daily chlorthalidone doses remain at 50 mg, further increments of Catapres of 0.1 mg or 0.2 mg per day can be made at intervals of 2 to 14 days depending on severity of hypertension. The usual daily dose of Catapres ranges between 0.2 and 0.8 mg. Studies indicate that 2.4 mg is the maximum effective daily dose, but doses as high as this have rarely been used.

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WARNING: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Actions: Catapres (clonidine hydrochloride): The mechanism of action appears to be central alpha-adrenergic stimulation as demonstrated in animal studies. This results in inhibition of bulbar sympathetic cardioaccelerator and sympathetic outflow from the brain. Other studies in humans have provided evidence of a reduction in plasma renin activity and the excretion of aldosterone and catecholamines. The exact relationship between these pharmacologic actions of Catapres (clonidine hydrochloride) in humans and its antihypertensive effect has not been fully elucidated at this time.

Chlorthalidone: The diuretic action of chlorthalidone is thought to be due to inhibition of sodium and chloride reabsorption in the proximal tubule.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been suggested that a withdrawal syndrome may be responsible for the hypertensive episodes. Symptoms of withdrawal hypertension, such as nervousness, agitation, headache, tremor, palpitation, nausea, vomiting, and occasionally hypertensive encephalopathy and cerebral hemorrhage with coma and convulsions have been reported. Withdrawal hypertension, if severe, should be treated promptly with appropriate antihypertensive therapy. Mild withdrawal hypertension may be controlled with sedation alone. Increased blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride, 0.1 mg + chlorthalidone, 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride, 0.2 mg + chlorthalidone, 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

References: 1. Becker, M. C.: Data on file at Boehringer Ingelheim Ltd. **2.** Belle, M. S.: Data on file at Boehringer Ingelheim Ltd. **3.** Hall, B. H.: Data on file at Boehringer Ingelheim Ltd. **4.** McDonald, R. L.: Data on file at Boehringer Ingelheim Ltd. **5.** Parsons, W. B., Jr.: Data on file at Boehringer Ingelheim Ltd. **6.** Russell, R. P.: Data on file at Boehringer Ingelheim Ltd. **7.** Winemiller, R. H.: Data on file at Boehringer Ingelheim Ltd. **8.** Yeh, B.: Data on file at Boehringer Ingelheim Ltd.

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SYMPOSIUM
Reperfusion During Acute Myocardial Infarction. Part I

Samuel Meerbaum, PhD, FACC and Eliot Corday, MD, FACC, *Guest Editors*

Introduction

SAMUEL MEERBAUM, PhD, FACC
ELIOT CORDAY, MD, FACC

Los Angeles, California

This Symposium appears at a time when there is substantial disagreement relative to the potential benefits or hazards of reperfusion after acute coronary occlusion. The basic question to be answered is: How does reperfusion affect jeopardized ischemic myocardium? The decision as to whether or how long after onset of an evolving acute infarction revascularization should be instituted needs to be based on applicable pathophysiologic data. It is our hope that the investigations reported on in this Symposium will provide information that will help develop criteria for applications of reperfusion.

There is increasing evidence that even after relatively brief periods of acute coronary occlusion the ischemic tissue is not capable of fully utilizing the blood reflow of reperfusion. Among possible mechanisms implicated in the reperfusion "no reflow" phenomenon are myocardial cell swelling, cell membrane dysfunction, interstitial edema and derangements of the coronary microcirculation. The degree of such reperfusion derangements and their consequences for global cardiac function depend on the preceding duration of ischemia. Studies quoted in this Symposium demonstrate that within 1 to 3 hours of acute coronary occlusion dysfunction in the ischemic myocardium is profound and may not be reversed by short periods of reperfusion. In fact, despite reestablishment of the patency of major coronary arteries, cardiac mechanical and metabolic function may not return for several hours, and hemorrhagic infarction may supervene. Thus, the early period of reperfusion is often associated with a state of hazardous metabolic, electrophysiologic and mechanical dysfunction, which might explain observed failures of surgical revascularization after acute myocardial infarction. On the other hand, current experimental studies indicate that 1 to 2 weeks of reperfusion, even after 3 to 4 hours of coronary occlusion, can lead to a substantial return of cardiac function and significant saving of myocardium.

Clinical results of revascularization performed during acute infarction are extremely difficult to interpret, in part because of a lack of control subjects and generally unsatisfactory classification of a complex patient population into subsets suitable for data analysis. The rationale of applying bypass surgery is based on the expectation of saving jeopardized but still viable ischemic myocardium by correcting a severe imbalance between regional myocardial oxygen demands and supply. Histologic studies in man have indicated that a substantial portion of the acutely ischemic zone becomes necrotic if it remains untreated for 24 to 48 hours. Experimental studies have revealed even earlier resolution of the fate of the jeopardized ischemic myocardium. Depending on the mode and degree of coronary obstruction, the extent of preexisting collateral vessels and prevalent myocardial stress, irreversible damage to the subendocardial layer of the ventricular wall is often noted with coronary occlusion of 40 minutes or longer. Necrosis of as much as 60 percent of the regionally ischemic left ventricle may be expected in 3 to 4 hours of occlusion, and 80 to 90 percent is lost after 24 hours of occlusion. Thus, if therapy is to lead to significant salvage of myocardium, it must be initiated between 40 minutes and 4 hours after the onset of acute infarction. This short period of myocardial viability presents a formidable clinical deadline to revascularization treatment of acute infarction. Temporary pharmacologic or mechanical modes of treatment might be instituted to buy time and avoid serious myocardial damage until the surgical team can be mobilized.

The validity of transferring information from animal experiments to the clinical setting may be questioned. However, such data have often been useful in elucidating related pathophysiologic mechanisms and providing guidelines for applying interventions.

Address for reprints: Eliot Corday, MD, Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles, Calif. 90029.

There is no shortage of research studies on reperfusion, but these have been plagued by a dearth of end points required to characterize explicitly and unequivocably the processes of ischemia and infarction and interventions. Inadequate markers hinder the definition of effectiveness of reperfusion, which otherwise might serve as an ultimate control in comparative evaluations of other modes of treatment. The heterogeneity of contributions to this Symposium reflects the current patchy knowledge and variety of questions surrounding reperfusion. Although this Symposium may not resolve the central issues of criteria for revascularization and optimal markers for its assessment, the contributors share a common objective of providing new insights and clarifications.

Summary of Symposium Papers

The Symposium begins with a brief paper by Krug, who has previously reported on coronary reperfusion in cats. Utilizing hydrogen ion concentration in ischemic zone tissue as an end point, he presents indirect observations of myocardial viability after acute occlusion of the proximal left anterior descending coronary artery. Reperfusion after 30 minutes of occlusion resulted in full return to normal pH values. After coronary occlusion exceeding 45 minutes, an "acid reaction" during the first minutes of reperfusion indicated persisting ischemia, presumably due to the "no reflow" phenomenon. After 90 minutes of reperfusion the reperfused region exhibited an "alkaline reaction" (pH ~7.4), particularly in the subendocardium, that correlated with enzymatic and histologic alterations characteristic of myocardial necrosis. After 180 minutes of coronary occlusion, the alkaline reaction was limited to a small border zone.

The nature of the metabolic changes during the first 2 hours of reperfusion was examined by Kane et al. in a series of pigs with 15 to 180 minutes of occlusion of the mid-left anterior descending coronary artery. Markers of myocardial viability included mitochondrial function, oxygen extraction, epicardial electrocardiographic S-T segments and distribution of tritiated digoxin. Within the first minutes of reperfusion after 1 or more hours of coronary occlusion, there were signs of hyperemia and improved regional kinesis, but soon thereafter (15 minutes or more) the ischemic zone became akinetic and noncompliant. After 2 hours of reperfusion following 1 hour of occlusion, regional mitochondrial function was severely impaired, myocardial oxygen extraction significantly reduced and tritiated digoxin stratified. Kane et al. noted that the S-T segments rose steeply after occlusion, but tended to return to control levels over 3 hours of coronary occlusion. Generally, epicardial S-T segment elevations in the ischemic zone diminished markedly with reperfusion, but after temporary occlusion in excess of 1 hour, the electrocardiogram exhibited a distinct loss of R waves and significant Q waves.

The problem of electrocardiographic and enzyme markers of myocardial ischemia or infarction is dealt with by Blumenthal et al., who performed open chest studies in dogs with 1 to 3 hours of occlusion of the left anterior descending coronary artery followed by 2 hours of reperfusion. A correlation was established between the appearance of Q waves and a sharp rise in coronary sinus serum enzymes, creatine phosphokinase (CPK) and glutamic oxaloacetic transaminase (GOT) after reperfusion. The usual delay in appearance of elevated enzyme levels and new Q waves after acute infarction does not necessarily indicate delayed necrosis; rather, it may simply reflect limited blood circulation within the ischemic region. Epicardial S-T segments most often returned to control levels after reperfusion, but in some instances decreased significantly during the preceding occlusion. Hence, the potential use of S-T segment elevation as a marker remains unclear. Two other experimental markers, namely, regional contraction force and reactive hyperemia, proved useful in assessing the effectiveness of reperfusion after periods of coronary occlusion. Blumenthal et al. conclude that myocardial viability may be limited to less than 2 hours of occlusion.

Sharma et al. provided ultrastructural evidence of myocardial derangements in the early phase of reperfusion after coronary occlusion. Histochemical study of specially prepared tissue samples revealed that 1 hour of reperfusion after 60 to 90 minutes of occlusion failed to return creatine phosphate toward control levels, while adenosine triphosphate and total nucleotide concentrations decreased further. Electron microscopic analysis indicated that the reperfusion resulted in swelling of sarcoplasmic reticulum, mitochondrial damage and gross contraction of myofibrils. Impairment of myocardial cell membranes was inferred from significant increases in coronary sinus blood enzyme levels noted immediately after reperfusion.

Measurement of regional mechanics was employed by Puri in a study addressed to the important question of late versus early reperfusion after various periods of coronary occlusion. Utilizing a strain gauge-tipped catheter probe that measures myocardial fiber shortening, Puri attempted to map the central and border zones of ischemia. He found that whenever myocardial blood flow was returned to the ischemic zone within 45 minutes, there was full and prompt resumption of contraction. With coronary occlusions lasting 1 hour, contraction returned gradually but completely after 2 weeks. With 2 or 3 hours of occlusion, only 60 to 75 percent of the reperfused zone was contracting after prolonged reperfusion. After 4 to 5 hours of occlusion, even extended reperfusion failed to restore partial contraction.

The effectiveness of reperfusion was studied in the intact conscious dog by Mathur et al. An implanted balloon cuff provided coronary occlusion for up to 5 hours, and subsequent reperfusion was maintained for up to 7 days. Occlusion of the proximal left anterior descending coronary artery led to expected hemodynamic and metabolic derangements. Immediately after reperfusion, following coronary occlusion

of more than 2 to 3 hours' duration, Mathur et al. noted striking and persistent arrhythmias, Q waves, hemodynamic dysfunction, regional left ventricular dyskinesia and diminished oxygen extraction. Infarct size was assessed and appeared to correlate with the duration of the occlusion. It was concluded that a reperfusion period of 1 week after more than 2 hours of occlusion in conscious dogs fails to prevent functional deterioration and is associated with a higher mortality rate.

In a similar study performed by Costantini et al. an intracoronary occlusion-reperfusion model in anesthetized dogs was used to investigate regional myocardial metabolism and detailed histopathology to provide insights into the effects of early and prolonged (7 days) reperfusion. The early phase of reperfusion following 3 hours of occlusion of the proximal left anterior descending coronary artery was characterized by persisting dysfunction, measured in terms of left ventricular ejection fraction, as well as by regional ischemic zone balances of oxygen, lactate and potassium. However, when compared with the persisting dysfunction and large infarcts observed in a control series with 7 days of permanent occlusion, there was an average 50 percent reduction in infarct size and return of cardiac function in animals undergoing 7 days of reperfusion. However, Costantini et al. emphasize that one third of the reperfused hearts showed no reduction in infarct size.

Corday et al. present evidence of functional and morphologic alterations in zones of the myocardium that are remote from an acutely ischemic region and are therefore often considered to be uninvolved. A 3 hour occlusion of the left anterior descending coronary artery was found to be associated with metabolic derangements as well as microinfarction in the remote myocardium. Reperfusion did not seem to reduce the number of microinfarcts. Since these remote segments of the heart are vital to global cardiac performance during infarction and revascularization, it is suggested that these zones should also be considered jeopardized.

Bolooki et al. address themselves to clinical evidence and supplement their study of patients with selected dog experiments. Utilizing left ventriculography for determination of left ventricular volume and ejection fraction, along with hemodynamic measurements and assessment of infarct size, they studied in dogs occlusion of the left anterior descending artery lasting up to 4 hours followed by 7 days of reperfusion. Only hearts with coronary occlusion of less than 2 hours' duration benefited from reperfusion. Reperfusion after 3 to 4 hours of occlusion resulted in infarcts and left ventricular dyskinesia equal to or greater than those measured after a 7 day permanent occlusion. The patient population was subdivided into groups receiving revascularization within less than 4 or within 8 hours from the onset of acute myocardial infarction. Analysis of data was difficult, but it appeared to Bolooki et al. that after 4 hours from the onset of an acute myocardial infarction, reperfusion may no longer provide benefits and may even precipitate hazardous derangements.

The quantitative differences in the reported reperfusion data are not surprising in view of differences in species and preparations (for example, open versus closed chest) and the normally encountered variability in experimental studies of coronary occlusion. One may conclude that in the dog derangements of the myocardium will appear early during reperfusion after 1 hour of occlusion, and that substantial irreversible damage must be expected when reperfusing after 2 to 3 hours of occlusion. The first few hours of reperfusion are clearly critical since there is a limited reflow, and severe derangements in mechanical and metabolic function persist, together with ominous arrhythmias. Nonetheless, 1 to 2 weeks of reperfusion after occlusion of as long as 3 hours can generally normalize function and provide substantial saving of myocardium.

There are several clinical implications. The observed myocardial derangements of reperfusion after coronary occlusion may account for the variability of results when clinical revascularization is applied during an evolving infarction. If such revascularization is to be effective, it must be started within a few hours of the onset of acute infarction. This raises practical questions relative to rapid mobilization of the angiographic-surgical team for earliest possible intervention. The studies of this Symposium indicate that proper monitoring and medical treatment should be available throughout the early period of reperfusion, lest severe arrhythmias and functional derangements escalate to severe hypotension and cardiogenic shock. In applying revascularization to an acute infarction, treatment of viable but jeopardized myocardium becomes a global task. Finally, reliable assessment of infarct size represents a major challenge that must be met to provide conclusions on the effects—and effectiveness—of reperfusion.

Alterations in Myocardial Hydrogen Ion Concentration After Temporary Coronary Occlusion: A Sign of Irreversible Cell Damage

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Alterations of hydrogen ion (H^+) concentration in the myocardium of 60 cats were determined before release of coronary ligation of 30, 45, 60, 90 or 180 minutes' duration, or 5, 30 and 90 minutes after release of the occlusion, by pressing pH indicator paper on unfixed frozen heart sections. The H^+ concentration had clearly increased (pH <6.0) in a transmural extension in the left ventricle before release of the coronary ligature. This elevated H^+ concentration persisted some time in the subendocardial region despite release of the coronary occlusion, thus proving that the so-called no reflow phenomenon exists in involved myocardium after temporary coronary occlusion. A diminished H^+ concentration (pH 7.4) was found in the border zone between the acid-reacting area and the normal muscle when the coronary occlusion lasted 180 minutes before release of the ligature or 30 minutes after release of the occlusion when the previous period of temporary occlusion had been longer than 30 minutes. Although areas manifesting an acid reaction vanished or diminished in size after release of coronary occlusion, the extent of alkaline-reacting zones showed no reduction in size, and muscle cell necrosis developed in these alkaline-reacting areas. It is assumed therefore that an alkaline reaction of the myocardium is an early sign of irreversible muscle cell damage.

The possibility of surgical treatment of acute myocardial infarction[1] has intensified interest in clarifying questions pertaining to the reversal of ischemic myocardial damage by revascularization. It has long been known that hydrogen ion (H^+) concentration in the myocardium increases immediately after the onset of ischemia[2] and diminishes later in the course of heterolytic processes.[3] In an attempt to answer some unresolved questions concerning these changes, we examined the alterations of H^+ concentration in involved myocardium after temporary coronary occlusion.

Methods

Sixty-three unselected cats, weighing 1.5 to 2.5 kg, were anesthetized with sodium pentobarbital (25 mg/kg body weight). The state of anesthesia was maintained by repeated injections of pentobarbital (10 mg/kg). Rectal temperature was determined by thermometer, and the experimental cats' temperature was maintained by electric blanket. Respiration was maintained through an endotracheal tube attached to a respirator pump. Left thoracotomy and pericardiotomy were performed. In 60 cats the anterior descending branch of the left main coronary artery (together with the accompanying vein) was ligated 2 to 3 mm distal to its origin for a duration of 30, 45, 60, 90 or 180 minutes. In these five groups, the beating heart was excised for study under four conditions: before release of coronary occlusion or 5, 30 or 90 minutes after release of the ligature. Three animals were used in each group.

The excised heart was frozen immediately, and cross sections, 40 μ thick, were cut from the unfixed tissue by cryostat. pH indicator paper (Merck AG, Darmstadt, West German Federal Republic) with pH ranges of 5.4 to 7.0 and 6.8 to 8.0 was pressed onto just-thawing unfixed cryostat sections of the

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hearts. In this way, the region of ischemic damage in the myocardium could be demonstrated immediately after the onset of ischemia by different degrees of discoloration of the pH indicator paper.[4,5]

Results

Normal cardiac muscle had a pH value of approximately 6.8. In the three control animals without coronary occlusion there were no zones with a hydrogen ion concentration that deviated from this figure.

H^+ Before Release of Coronary Occlusion (Fig. 1)

The hydrogen ion concentration rose (pH <6.0) in the anterior wall of the left ventricle in a transmural extension when the coronary occlusion lasted 30, 45, 60 or 90 minutes (Fig. 1 and 2A). However, a diminished H^+ concentration (pH 7.4) was found in a small border zone between the acid-reacting area and the normal heart muscle when the coronary occlusion lasted 180 minutes.

H^+ After Release of Coronary Occlusion (Fig. 1)

Occlusion of 30 minutes' duration: No zones with an H^+ concentration that deviated from the normal pH value of 6.8 were found 5, 30 or 90 minutes after release of the ligature (Fig. 1).

Occlusions of 45 and 60 minutes' duration: The acid-reacting region diminished significantly after release of the coronary ligature and a change in H^+ concentration took place in the inner third of the ventricular wall (Fig. 1). Although a continuing acid reaction was found subendocardially 5 minutes after release of the coronary ligature (Fig. 2B), 30 and 90 minutes later, the inner third of the ventricular wall showed an alkaline reaction (pH 7.4, Fig. 2C).

Occlusion of 90 minutes' duration: The acid-reacting region was still diminished after release of the ligature but to a lesser degree than after temporary coronary occlusions of 45 and 60 minutes' duration (Fig. 1). An acid reaction in the center of the anterior wall and a broad alkaline-reacting border zone were found 30 minutes after release of the ligature (Fig. 2D). However, 90 minutes after release of the occlusion the entire inner half of the anterior ventricular wall had a diminished H^+ concentration (pH 7.4).

Occlusion of 180 minutes' duration: The transmural area that showed H^+ alterations did not diminish after release of the coronary ligature (Fig. 1). The H^+ concentration decreased in the entire anterior wall of the left ventricle, but 5 and 30 minutes after release of the ligature there were still acid-reacting areas in the center of the anterior wall. This finding indicates that the alkalization of the previous acid-reacting zones took effect from the periphery to the center. However, 90 minutes after removal of the ligature the entire anterior wall produced an alkaline reaction (Fig. 2E).

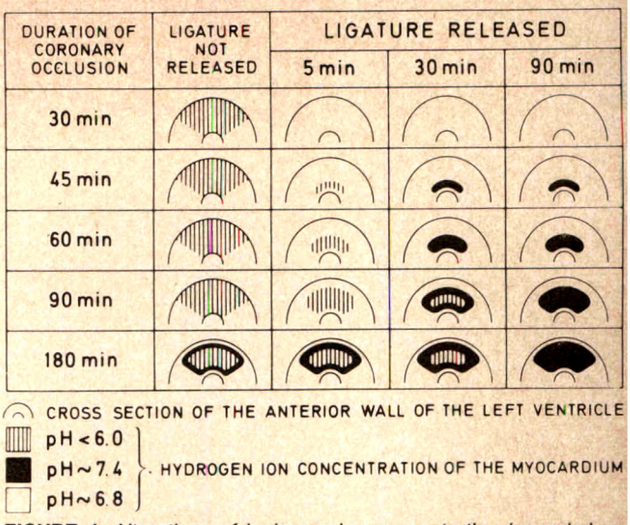

FIGURE 1. Alterations of hydrogen ion concentration (recorded as pH value) in the myocardium of 60 cats after temporary coronary occlusion. Three animals were used in each of the 20 groups shown.

Discussion

As these findings show, alteration of myocardial hydrogen ion concentration by ischemia can be detected by freezing the tissue and pressing a just-thawing tissue section onto pH indicator paper. In this way the intracellular H^+ concentration can be determined because the freezing and thawing process destroys the cells. This procedure makes possible delineation in the heart of early myocardial infarction, which cannot be done by any other available method.[6] The H^+ concentration rose markedly in a transmural extension of the anterior wall of the left ventricle after occlusion of the anterior branch of the left coronary artery. It has long been known that acidification takes place in the myocardium after the onset of ischemia because acid metabolites (predominantly lactic acid) are accumulated during anaerobic glycolysis.[2] The data reported here show further that this acidification of the myocardium is reversible when the blood supply is reestablished by release of the coronary ligature.

The acid-reacting areas vanished completely after release of coronary occlusion of 30 minutes' duration or diminished significantly after release of coronary occlusion of 45 and 60 minutes' duration. But the findings clearly show (Fig. 2B) that an acid-reacting area is still demonstrable subendocardially after release of coronary occlusion of 45 minutes' duration; that is, despite release of the coronary ligature, blood flow is not reestablished in these zones. This conclusion is possible because previous investigations[5,7] have shown that blood flow is heavily disturbed and often nonexistent in myocardial areas with increased H^+ concentration. Therefore, in contrast to the opinion of Jennings et al.,[8] these findings prove the existence of the so-called no reflow phenomenon[9] after temporary myocardial ischemia of only 45 minutes' duration.[7] This no reflow phenomenon indicates that there is persistent ischemia in involved myocardium despite release of the coronary occlusion and that it may be an important cause of cell necrosis. Further

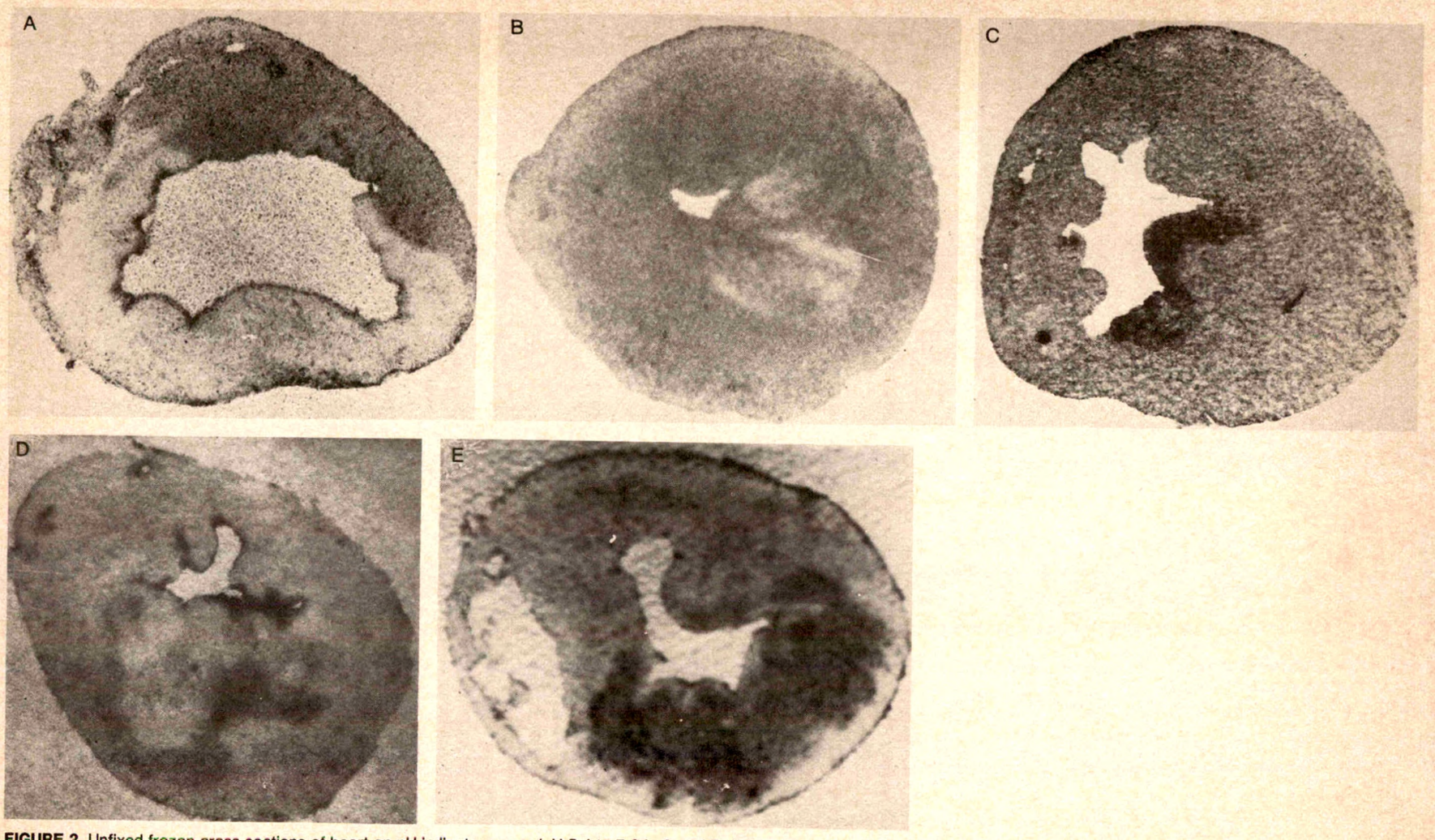

FIGURE 2. Unfixed frozen cross sections of heart on pH indicator paper (pH 5.4 to 7.0 in **A** and **B**, 6.8 to 8.0 in **C** to **E**). **A,** 60 minutes after coronary ligation before release of the ligature. The hydrogen ion (H^+) concentration is elevated (pH <6.0) in a transmural extension of the anterior wall of the left ventricle, as indicated by yellow discoloration of the indicator paper (**light area** in figure). **B,** 5 minutes after release of ligation of 45 minutes' duration. The H^+ concentration is still increased (pH <6.0) in the inner third of the anterior wall of the left ventricle. **C,** 90 minutes after release of ligation of 45 minutes' duration. The H^+ concentration is diminished (pH 7.4) in the inner third of the anterior wall of the left ventricle, as indicated by green discoloration of the indicator paper (**dark area**). **D,** 30 minutes after release of coronary ligation of 90 minutes' duration. A persistent acid-reacting region (**light area**) is shown in the center of the anterior wall; the border zone reveals a diminished H^+ concentration (pH 7.4, **dark area**). **E,** 90 minutes after release of ligation of 180 minutes' duration. The H^+ concentration is diminished in the entire anterior wall of the left ventricle (pH 7.4, **dark area**).

investigations are needed to determine whether this phenomenon is treatable.

Myocardial alkalinity after coronary occlusion and reperfusion: Alkalization of the myocardium was found 180 minutes after coronary occlusion in the border zone between the normal muscle and the area with increased H^+ concentration or 30 and 90 minutes after a temporary occlusion of 45, 60 or 90 minutes' duration. These alkaline-reacting areas did not vanish or diminish. The alkalization of the tissue is caused by penetration of plasma bicarbonate and heterolytic processes.[3,10] It was possible to show by histologic and enzyme histochemical methods that necrosis of the muscle cells occurs very rapidly in those zones that show an alkaline reaction, and myocardial infarctions developing after temporary coronary occlusion of 45, 60 or 90 minutes' duration occurred in the same site in the ventricular wall[11] as the alkaline-reacting areas. From these results, it can be assumed that the presence of an alkaline-reacting area in the myocardium indicates that the heart muscle cells in this region are irreversibly damaged; that is, in an alkaline-reacting area the so-called point of no return for the muscle cells has been reached after the onset of ischemia. In the cats' hearts, this sign of irreversible cell damage was first ascertained 3 hours after permanent coronary occlusion but, after temporary coronary ligation of 45 minutes' duration, alkaline-reacting areas were first seen 30 minutes after release of the ligature.

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Mitochondrial Function, Oxygen Extraction, Epicardial S-T Segment Changes and Tritiated Digoxin Distribution After Reperfusion of Ischemic Myocardium

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This study examines the effect of 2 hours of reperfusion on transiently ischemic myocardium in pigs. Indexes of myocardial viability measured were mitochondrial function, oxygen extraction, epicardial S-T segment change and distribution of tritiated digoxin. Results were as follows: (1) Mitochondrial function was markedly impaired in the reperfused area after 60 minutes or more of coronary occlusion. The defect would seem to be a block in electron flow near site I, which can be partially bypassed with succinate. (2) An apparent inability of the reperfused myocardium to extract oxygen did not improve with 2 hours of reperfusion. (3) Epicardial S-T segment mapping suggested that necrosis occurred during reperfusion. (4) There was an altered distribution of tritiated digoxin in the reperfused area. The results show that reperfusion for 2 hours did not improve myocardial viability after 60 minutes or more of ischemia.

Recent reports[1–3] have demonstrated that reperfusion of acutely ischemic myocardium may be associated with deleterious effects. Some studies have demonstrated a "no reflow" phenomenon in transiently ischemic myocardium similar to that observed in the brain and kidneys.[4,5] Although earlier experiments have shown that a coronary artery may be ligated for up to 3 hours before blood flow is restored without development of myocardial necrosis, more recent studies have suggested that reperfusion of an ischemic area alters the metabolism of the ischemic myocardium and may even hasten necrosis.[1,2] Thus, the optimal time for reperfusion of acutely ischemic myocardium and its effect on cardiac metabolism are not well established.

In cardiac muscle the mitochondria, which make up at least 20 percent by dry weight of the cell,[6] consume oxygen to produce adenosine triphosphate (ATP) by oxidative phosphorylation. Adenosine triphosphate is then used by the myocardium as the energy source for contraction and other cellular functions.[7] Previous studies have suggested that mitochondria are very susceptible to hypoxia.[8] Altered mitochondrial function, then, may be the mechanism of irreversible changes that take place in ischemic myocardium.[9] The purpose of this study was to examine mitochondrial function, myocardial oxygen extraction, epicardial S-T segment mapping and distribution of tritiated digoxin in myocardium made transiently ischemic and then reperfused.

Methods

Pigs were chosen as the experimental model because the major coronary distribution, collateral circulation and blood supply to the conduction system

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are virtually identical to those of man.[10–12] Forty-six mature farm pigs of either sex, weighing 70 to 120 lb, were fasted for 18 hours and then anesthetized with 6 percent pentobarbital administered intravenously. A tracheostomy was performed and respirations maintained with a Harvard pump using room air supplemented with 100 percent oxygen to maintain the arterial partial pressure of oxygen (PaO_2) over 100 mm Hg. A midline sternal splitting thoracotomy was performed and the heart suspended in a pericardial cradle exposing the distribution of the left anterior descending coronary artery. Central aortic and left ventricular pressures and lead II of the electrocardiogram were continuously monitored.

The left anterior descending coronary artery was reversibly occluded, with use of a nontraumatic rubber ligature, at its midportion after the first or second diagonal branch for intervals of 15 to 180 minutes. Complete occlusion in each case was evidenced by the appearance of a nonpulsatile, nondistended artery distal to the occlusion and nondistended veins draining the ischemic area, and by the immediate appearance of cyanosis and bulging of the ischemic segment. Forty-two animals then had reperfusion of the ischemic zone of the myocardium for an additional 2 hours. Four animals underwent coronary occlusion for 180 minutes without reperfusion. The coronary vein was preserved in each case and not ligated.

Ventricular arrhythmia secondary to coronary occlusion was treated with minimal effective doses of lidocaine or electrical countershock using an American Optical defibrillator set at 30 to 50 watt seconds. Although no attempt was made to heparinize the animals, 1,000 to 2,000 units of heparin was placed in each liter of flush solution for the arterial lines.

Epicardial S-T segment mapping was performed every 30 minutes over three areas of normal left ventricle and five areas of ischemic tissue with use of a soft spring steel electrode with a spherical silver tip. This electrode had a surface area contact of 2 mm and caused minimal pressure artifact. S-T segment elevation and R wave amplitude were quantitated in nine animals.

Blood samples for determining oxygen content and pH were obtained from the large coronary vein draining the ischemic area just before occlusion and then serially during the reperfusion period in nine animals. These were compared with simultaneously obtained samples from the left ventricular chamber.

After release of the ligature, 0.5 mg of tritiated digoxin was injected intravenously to serve as a marker of blood flow and perhaps as a measure of cellular viability in the area of ischemia.[13,14]

At the end of each 2 hour period of reperfusion, 2.5 to 5 cc of 10 percent alphazurine 2G blue dye was injected intravenously in order to identify areas of the myocardium that were not well perfused. This dye stained perfused and presumably viable tissue a vivid blue and was not taken up by ischemic tissue.[15] Immediately after injection of the dye, the heart was removed from the chest and taken to the cold room where samples were excised from normal and reperfused areas of the left ventricle using the surface anatomy and dye staining as guidelines.

The tissue samples were minced and homogenized by methods similar to those previously outlined.[16] Mitochondria were separated and suspended in a medium containing 0.25 molar sucrose; 0.001 molar neutralized ethylenediaminetetraacetic acid (EDTA); 0.01 molar Tris buffer at pH 7.4; 7.5 millimolar potassium phosphate at pH 7.4; and 0.01 molar substrate in a final volume of 3 ml. Either glutamate

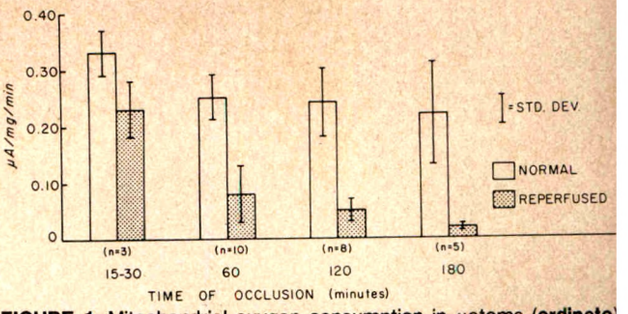

FIGURE 1. Mitochondrial oxygen consumption in μatoms (**ordinate**) using glutamate substrate during state 3 respiration in 26 animals. Mitochondria from normal areas of the left ventricle (**open bars**) are compared with mitochondria from reperfused areas (**dotted bars**). The occlusion period was 15 to 180 minutes. All animals had 120 minutes of reperfusion. n = number of animals; STD. DEV. = standard deviation.

(0.01 molar), succinate (0.01 molar) or a mixture of pyruvic acid (0.005 molar) and L-malic acid (0.005 molar) was used as a substrate (this latter combination being referred to as malate). Oxidative phosphorylation studies were performed in duplicate by a polarographic method[17] and were completed within 90 minutes after the death of the animals. Adenosine diphosphate (ADP) was added to each reaction mixture to give a rapid burst of state 3 respiration. In six animals, dinitrophenol (final concentration 6×10^{-5} molar) was used as an uncoupler of respiration and oligomycin (final concentration 3×10^{-6} molar) added as an inhibitor of phosphorylation. In each experiment, mitochondria from the normal areas of the left ventricle were tested simultaneously with mitochondria from the reperfused area.

Indexes of mitochondrial function obtained were: mitochondrial oxygen consumption in μatoms of oxygen consumed per milligram of mitochondrial protein per minute during state 3 respiration, a measure of the electron transport capability[18]; ADP:O ratio, the ratio of μmoles of adenosine diphosphate phosphorylated to atoms of oxygen consumed, a measure of efficiency of adenosine triphosphate production[19]; and respiratory control ratio, the ratio of oxygen consumed in the presence of adenosine diphosphate to oxygen consumed after complete phosphorylation of the adenosine diphosphate, a measure of tightness of coupling.[19] Mitochondrial protein content was determined by a standard method[20] with attempts being made to achieve 2 mg/ml of mitochondrial protein. Adenosine diphosphate assays were determined spectrophotometrically.[21] Tissue and serum tritiated digoxin levels were measured as previously described.[22]

Results

General observations: After coronary occlusion myocardium supplied by the left anterior descending coronary artery ceased contracting, became cyanotic and bulged within seconds. These changes persisted throughout the occlusion. Arterial blood pressure, heart rate and left ventricular end-diastolic pressure were not significantly different from control values.

After release of the ligature and reperfusion, the distal left anterior descending coronary artery became distended. The reperfused epicardium lost its cyanotic appearance within 30 seconds to 1 minute o

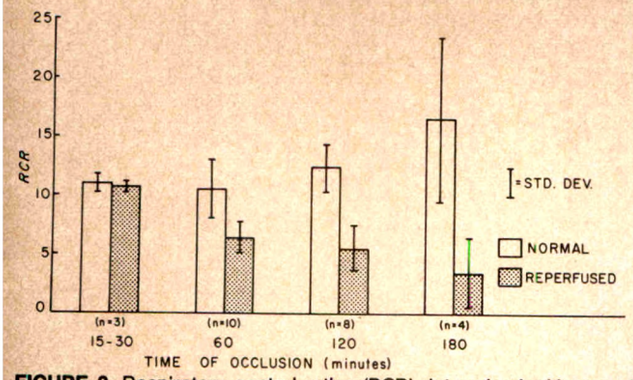

FIGURE 2. Respiratory control ratios (RCR) determined with use of glutamate substrate in 25 animals. Mitochondria from normal areas of the left ventricle (**open bars**) are compared with mitochondria from reperfused areas (**dotted bars**). The occlusion period was 15 to 180 minutes. All animals had 120 minutes of reperfusion.

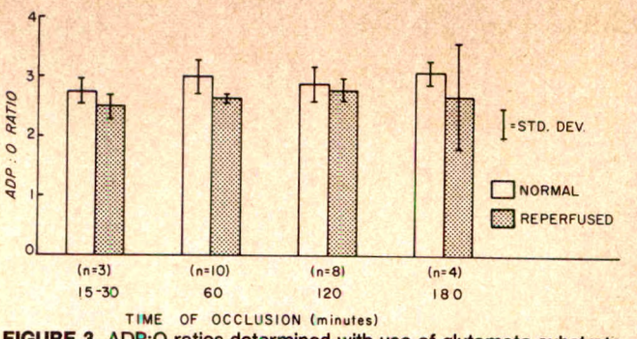

FIGURE 3. ADP:O ratios determined with use of glutamate substrate in 25 animals. Mitochondria from normal areas of the left ventricle (**open bars**) are compared with mitochondria from reperfused areas (**dotted bars**). The occlusion period was 15 to 180 minutes. All animals had 120 minutes of reperfusion.

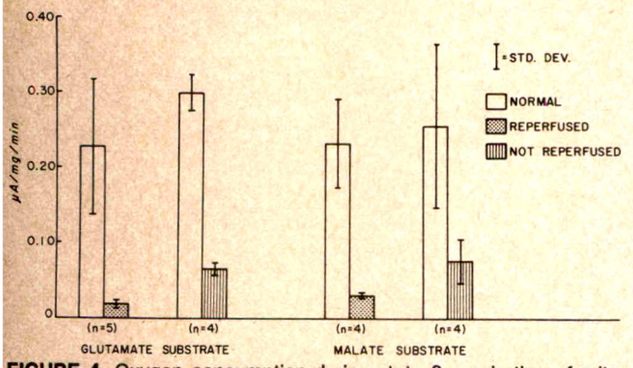

FIGURE 4. Oxygen consumption during state 3 respiration of mitochondria from normal areas of the left ventricle (**open bars**), and areas of the left ventricle with 180 minutes of occlusion and 120 minutes of reperfusion (**dotted bars**) is compared with that of mitochondria from animals that had 180 minutes of occlusion but no reperfusion (**striped bars**). Determinations were made with use of glutamate and malate substrates.

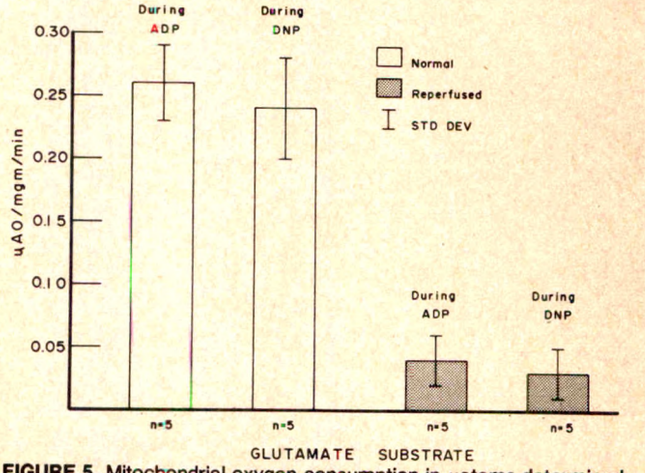

FIGURE 5. Mitochondrial oxygen consumption in μatoms determined with use of glutamate substrate during phosphorylation (addition of adenosine diphosphate [ADP]) and uncoupling (addition of dinitrophenol [DNP]) in normal and reperfused preparations. Rates are similar with adenosine diphosphate and dinitrophenol in normal and in reperfused mitochondria.

release of occlusion and became hyperemic when compared with normal areas of the left ventricle. Bulging of the involved segment likewise diminished within 30 seconds to 1 minute; however, over a period of 5 to 15 minutes the muscle became akinetic and firm rather than regaining contractile function. Reperfusion for 2 hours did little to change the gross appearance.

After removal of the heart, the reperfused area could be recognized by its firm texture as opposed to the soft and pliable texture of normal myocardium or myocardium from hearts with 180 minutes of occlusion and no reperfusion.

Mitochondrial function: Figure 1 shows the effect of different periods of occlusion on mitochondrial oxygen consumption by mitochondria from normal and reperfused areas of the left ventricle, as determined with use of glutamate substrate in 26 animals. After 15 to 30 minutes of occlusion, there was a slight decrease in oxygen consumption in the reperfused mitochondria ($P < 0.05$) (Student's t test). By 60 minutes the difference was highly significant ($P < 0.001$). Further impairment was evident with longer periods of occlusion. Studies with malate substrate gave similar results. Figure 2 shows the results of different periods of occlusion on the respiratory control ratio again with use of glutamate substrate. Although there was little difference after 15 to 30 minutes of occlusion, occlusion periods longer than 60 minutes resulted in a significant decrease in the respiratory control ratio ($P < 0.001$). ADP:O ratios, a measure of efficiency of adenosine triphosphate production, were not significantly different even with occlusion of up to 3 hours (Fig. 3). That reperfusion itself may have contributed to an inhibition of oxidative phosphorylation is shown in Figure 4, which compares oxygen consumption of mitochondria from normal and reperfused tissue with that of mitochondria from animals that had identical periods of occlusion (180 minutes) but did not undergo reperfusion. When

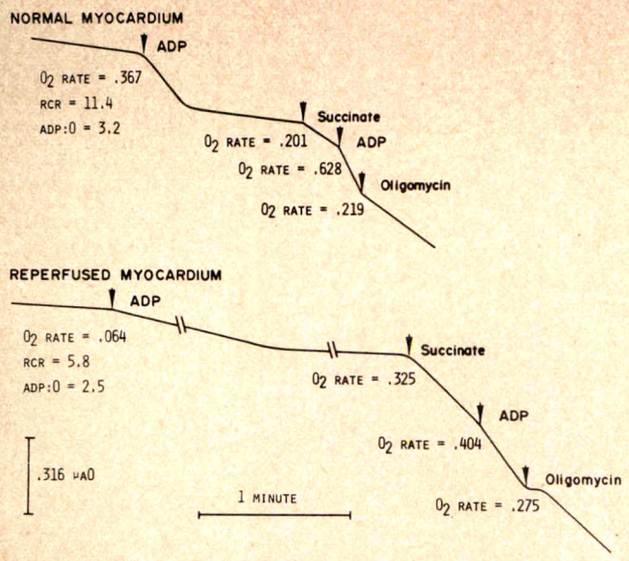

FIGURE 6. Simultaneous oxygen electrode tracings showing oxygen consumption by mitochondria from normal and reperfused myocardium in glutamate substrate. The occlusion period was 120 minutes. Addition of succinate markedly increased oxygen consumption in both normal and reperfused preparations. Oligomycin was added in a final concentration of 3×10^{-6} molar as an inhibitor of phosphorylation. ADP = adenosine diphosphate; ADP:O = ratio of micromoles of adenosine diphosphate phosphorylated to atoms of oxygen consumed; RCR = respiratory control ratio.

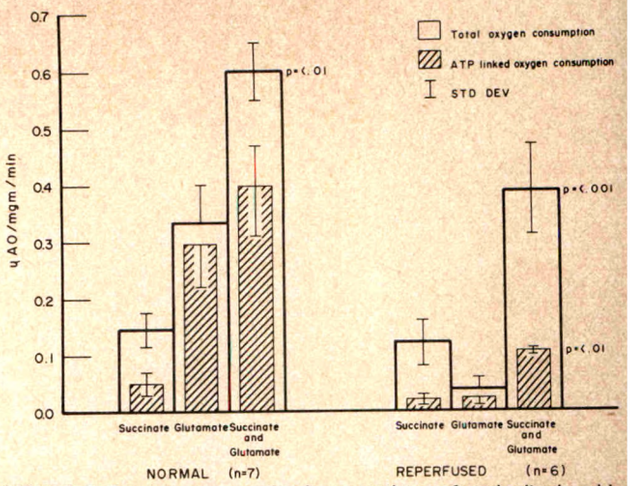

FIGURE 7. Oxygen consumption by normal reperfused mitochondria after addition of adenosine diphosphate (ADP) is compared using succinate and glutamate alone or in combinations as substrates. Adenosine triphosphate (ATP)-linked oxygen consumption is indicated by the **hatched bars.** Although total oxygen consumption is increased in both preparations by the addition of succinate, adenosine triphosphate-linked oxygen consumption was significantly greater with a combination of substrates in reperfused mitochondria.

studied with either glutamate or malate substrate, mitochondrial function was worse in the reperfused tissue ($P < 0.005$).

In six animals dinitrophenol (final concentration 6×10^{-5} molar) was used as an uncoupler of respiration (Fig. 5). The rate of oxygen consumption was the same during phosphorylation (addition of adenosine diphosphate) or uncoupling (addition of dinitrophenol) in the normal mitochondria. Oxygen consumption was much less in the reperfused mitochondria but the rates were the same during phosphorylation or uncoupling. Results were similar in studies with malate substrate.

The diminished mitochondrial oxygen consumption and results with dinitrophenol as an uncoupler of respiration suggested that mitochondrial dysfunction was caused by a block in electron flow. Based on the theory that the block might be located at site I, succinate was used as a substrate either singly or in combination with glutamate and malate to attempt to bypass the electron transport chain block. Figure 6 illustrates the results obtained when succinate was used as a substrate in combination with glutamate. Figure 7 shows the oxygen consumption of mitochondria in seven such experiments together with data for succinate and glutamate used alone. The combination of glutamate and succinate resulted in a total oxygen consumption that significantly exceeded the sum of that produced individually by these substrates in mitochondria from normal ($P < 0.01$) or reperfused ($P < 0.001$) myocardium. Of particular interest is that the combination of substrates yielded more adenosine triphosphate-linked oxygen consumption* than was obtained, in sum, by the two substrates individually in mitochondria from reperfused myocardium ($P < 0.01$). In the mitochondria prepared from normal myocardium, the sum of adenosine triphosphate-linked oxygen consumption with the individual substrates is the same as that produced by the combination of succinate plus glutamate. The enhancement of total oxygen consumption and adenosine triphosphate-linked oxygen consump-

TABLE I

Regional Coronary Venous Oxygen and Arteriovenous Oxygen Difference During Reperfusion

Minutes After Reperfusion	Coronary Venous O_2 (mm Hg, mean ± SD)	Arteriovenous O_2 Difference* (% saturation, mean ± SD)
Control†	26.0 ± 10.1	53.0 ± 19.0
5	48.2 ± 5.9	31.5 ± 14.0
30	85.7 ± 28.7	4.8 ± 3.2
60	79.0 ± 14.9	3.9 ± 2.9
90	91.1 ± 19.0	3.3 ± 2.2
120	83.0 ± 23.3	4.6 ± 3.1

*Difference in oxygen saturation of coronary venous and left ventricular chamber samples.

†Before occlusion.

O_2 = oxygen; SD = standard deviation.

* Adenosine triphosphate-linked oxygen consumption was calculated by the difference in oxygen consumption before and after addition of adenosine diphosphate or by the difference between oxygen consumption with adenosine diphosphate and oligomycin.

tion was not seen in experiments using succinate in combination with malate.

Myocardial oxygen extraction: There was a highly significant rise in oxygen tension in the coronary vein draining the reperfused area with a reduction in arteriovenous oxygen difference (Table I). Grossly, the veins draining the reperfused area became red 5 to 10 minutes after reperfusion indicating that they were carrying arterialized blood. These findings persisted throughout the 2 hour period of reperfusion.

Epicardial S-T segment mapping: S-T segments were elevated in the ischemic area within minutes of occlusion but drifted toward control values later during the occlusion period (Fig. 8). Within 30 minutes of reperfusion, S-T segments returned to normal but there was a striking loss in R waves over the reperfused area with formation of significant Q waves. Results for nine animals are presented in Table II. There were no significant differences in results obtained from epicardial leads monitored at the marginal area of reperfusion.

Tritiated digoxin distribution: There were marked abnormalities in tritiated digoxin uptake in the reperfused area (Fig. 9) compatible with a failure of the reperfused myocardium to bind tritiated digoxin that was distributed to the area of decreased blood flow after reperfusion. Although there was little difference in the 15 to 30 minute occlusion group, in the groups with 60 minutes or more of coronary occlusion there was a highly significant decrease in tritiated digoxin concentration in the reperfused tissue ($P < 0.001$). Poor uptake of alphazurine dye also occurred in the reperfused area in animals with 60 minutes or more of coronary occlusion.

TABLE II

Epicardial S-T Segment Elevation and R Wave Over Involved Myocardium During Coronary Occlusion and Reperfusion

	S-T Segment Elevation (mm) (mean ± SD)	R Wave (mm) (mean ± SD)
Control (before occlusion)	0	9.4 ± 3.7
Minutes after occlusion		
15	8.1 ± 3.3	44.1 ± 12.2
30	16.3 ± 7.1	31.2 ± 13.1
60	17.1 ± 5.7	17.6 ± 9.8
90	14.8 ± 8.1	9.6 ± 8.3
120	11.2 ± 5.5	6.3 ± 7.9
Minutes after reperfusion		
15	3.2 ± 2.0	0.6 ± 1.0
30	1.0 ± 0.7	0
60	0	0
90	0	0
120	0	0

Abbreviations as in Table I.

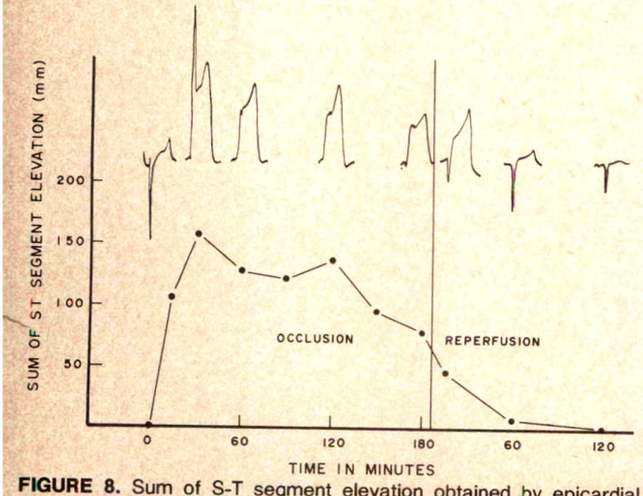

FIGURE 8. Sum of S-T segment elevation obtained by epicardial mapping over five areas of ischemic myocardium and representative electrocardiogram during occlusion and reperfusion. Note return of S-T segment to control levels and loss of R waves during reperfusion.

Discussion

Our results show that a severe metabolic derangement occurs in myocardium made ischemic for more than 60 minutes and then reperfused for 2 hours. There was marked functional impairment of mitochondria isolated from the reperfused area as compared with mitochondria from normal left ventricular tissue. Occlusion times greater than 60 minutes appeared to result in irreversible changes. The near normal ADP:O ratios with a decreased oxygen consumption are compatible with inhibition of phosphorylation rather than uncoupling and suggest a block in electron flow. The use of an uncoupler, dinitrophenol, confirmed that there was a block in electron flow. In mitochondria from reperfused myocardium a significant increase in total and adenosine triphosphate-linked oxygen consumption occurred with either succinate or succinate and glutamate substrates together, suggesting the block can be partially bypassed with succinate. The site of the block would thus seem to be near site I of the electron transport chain.

The increase in coronary venous oxygen tension and reduction in arteriovenous difference in the coro-

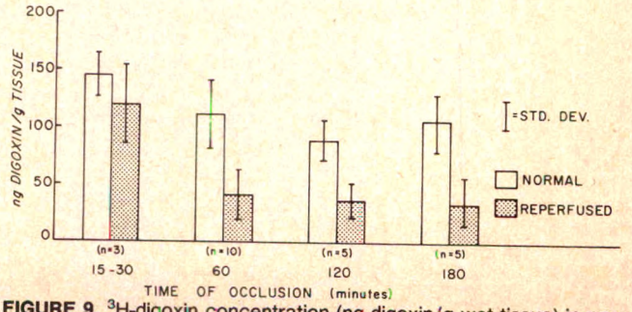

FIGURE 9. ^{3}H-digoxin concentration (ng digoxin/g wet tissue) in normal (**open bars**) and reperfused (**dotted bars**) myocardium is compared in 23 animals with 15 to 180 minutes of coronary occlusion and 120 minutes of reperfusion.

nary vein draining the reperfused area is compatible with arteriovenous shunting or, more likely, failure of the reperfused area of the left ventricle to extract oxygen. These findings correlated well with impaired mitochondrial function from this same area.

The results of epicardial S-T segment mapping show the reperfusion of ischemic myocardium was associated with a return of elevated S-T segments to control levels. However, formation of significant Q waves and impaired mitochondrial function in the reperfused area suggest the persistence of severe damage. Measurement of epicardial S-T segment changes alone did not indicate the true status of the myocardium after reperfusion. Formation of Q waves during reperfusion also suggests that accelerated damage may have occurred during the reperfusion period.

The failure of reperfused tissue to accumulate tritiated digoxin or vital dye may simply indicate a failure to restore blood to the area, or may be a further reflection of cellular damage. Impairment of mitochondrial function correlated with the altered distribution of tritiated digoxin and poor uptake of alphazurine 2G blue dye. Other investigators[13] have also reported a marked alteration in distribution of ^{3}H-digoxin or radioactive microspheres[23] by an infarcted and ischemic left ventricle and have suggested that ^{3}H-digoxin is a marker of blood flow. Although our study did not attempt to measure ^{3}H-digoxin concentration in the inner and outer layers of the left ventricular wall, it was evident from staining by the alphazurine dye that there was a marked defect in regional blood supply to the middle layers of myocardium, with the epicardium and endocardium generally staining evenly after reperfusion. These findings indicate a disturbance in circulation, especially to the innermost layers of the left ventricular wall, that persists after reperfusion. The abnormal mitochondrial function demonstrated in this area is therefore most likely the result of inadequate tissue perfusion with persisting ischemia.

These results agree with those reported by other observers. Krug,[24] using cats in reperfusion experiments, found that there were ischemic areas in the inner layer of the heart that could not be reperfused after coronary ligation of 30 to 45 minutes. Copeland et al.[7] showed that there were morphologic changes in dog heart mitochondria after 45 minutes of anoxia and that these changes were not reversed by up to 7 hours of reperfusion. Jennings et al.[25] likewise noted ultrastructural change and marked functional abnormalities in mitochondria isolated from ischemic dog papillary muscle after 60 minutes of coronary occlusion. Recently Lang et al.[1] reported profound changes in hemodynamics, metabolic function and morphologic structure in dog hearts after 3 hours of coronary occlusion followed by 5 hours of reperfusion. They concluded that reperfusion may not reverse hemodynamic and metabolic disorders induced by 3 hours of occlusion and that reperfusion may even have a detrimental effect, resulting in accelerated necrosis and deterioration of function. Banka et al.[26] demonstrated accentuation of contractile abnormalities after 2 hours of occlusion that appeared irreversible with reperfusion.

In summary, this study shows by a number of different measurements that reperfusion of transiently ischemic myocardium for 2 hours does not restore significant myocardial viability in that area. Mitochondrial function was markedly impaired after 60 minutes of coronary occlusion. The defect would seem to be a block in electron flow near site I that can be partially bypassed with use of succinate. There was an apparent inability of the reperfused myocardium to extract oxygen as evidenced by an increase in coronary venous oxygen tension and a decrease in arteriovenous oxygen difference. Epicardial S-T segment mapping provided evidence of necrosis during reperfusion, and there was a markedly altered distribution of tritiated digoxin and vital dye in the reperfused area compatible with a disturbance in blood flow or cellular integrity.

Clinical implication: If these results are applicable to the acutely infarcted myocardium in man, they suggest that revascularization for 2 hours or more will not salvage ischemic myocardium. Thus, the results of early surgical intervention as treatment for acute ischemia must be critically evaluated.

Acknowledgment

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Experimental Coronary Arterial Occlusion and Release

Effects on Enzymes, Electrocardiograms, Myocardial Contractility and Reactive Hyperemia

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After less than 1 hour of coronary arterial occlusion, the myocardium suffers irreversible changes as revealed by electron microscopy. Yet, the earliest clinical laboratory indexes of myocardial infarction—elevated serum enzyme levels and significant Q waves on the electrocardiogram—are not detected until at least 6 hours after coronary occlusion. To study the early period after coronary occlusion in the dog, occlusion of the left anterior descending coronary artery for 1 to 3 hours was followed by release, and coronary sinus and venous enzyme levels, the electrocardiogram and myocardial contractility from the infarcted area, and reactive hyperemia were monitored. Coronary sinus enzyme levels rose within 15 minutes after release of occlusion in half of the experiments with 1 to 1 1/2 hours and in all of those with 2 to 3 hours of occlusion, and this rise preceded the rise in venous levels by only 10 to 20 minutes. Significant Q waves appeared 15 to 30 minutes after release of occlusion as the serum enzymes were increasing. Thus, clinically, the delayed appearance of increased serum enzymes and significant electrocardiographic Q waves is probably largely due to a lack of circulation in the infarcted area rather than to prolonged survival time. Also, the venous enzyme level reflects the coronary sinus level minutes later. The presence of viable myocardium in the infarcted area was suggested by elevation of the S-T segment upon reclamping, and by residual myocardial contractility and retained capacity for reactive hyperemia. These findings occurred in some experiments even in the presence of a significant Q wave.

Coronary artery bypass surgery is still seeking its proper position in relation to traditional medical management of coronary artery disease. One area of current discussion is the applicability of this procedure to acute myocardial infarction.[1] After experimental coronary occlusion, the myocardium has been shown by electron microscopy to be irreversibly damaged in 1 hour or less.[2] Yet the accepted clinical laboratory criteria—elevation of serum enzyme levels and appearance of significant electrocardiographic Q waves—do not appear for many hours after coronary occlusion. Clearly, more knowledge of the genesis of these indexes is required.

Previous studies of acute experimental coronary occlusion have confirmed the delay in appearance of elevated serum enzyme levels and electrocardiographic Q waves. The loss of enzymes from the myocardium after coronary arterial occlusion has been monitored in three ways: (1) Serum levels have been measured in *delayed occlusion* experiments, in which a loop is placed around a coronary artery and closed 1 week later after the surgically induced increase in serum enzymes has subsided. (2) Serum levels have been determined after *bead embolization* of a coronary artery in closed chest dogs, thus avoiding any rise in enzyme levels due to operation; and (3) *myocardial enzyme content* has been determined at different intervals after

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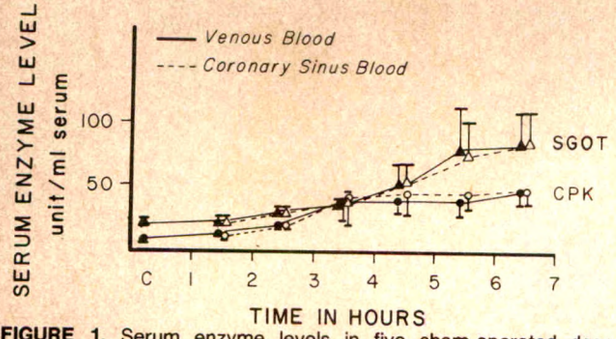

FIGURE 1. Serum enzyme levels in five sham-operated dogs. Values are expressed as mean ± standard error of the mean. Serum glutamic oxaloacetic transaminase (SGOT) in international units and serum creatine phosphokinase (CPK) in Sigma units are plotted against time from start of operation (C).

coronary occlusion. In *delayed occlusion,* serum glutamic oxaloacetic transaminase (GOT) and creatine phosphokinase (CPK) levels begin to rise in 4 to 6 hours and peak in 18 to 28 hours.[3–6] With *bead embolization,* which causes microinfarcts, serum GOT elevation appears earlier, in 3 to 5 hours, and also peaks sooner, in 9 to 23 hours.[7,8] After coronary arterial ligation, *myocardial GOT content* begins to decrease in 4 hours and is reduced only 40 to 50 percent in 24 hours.[3,9] The known delay in the development of significant Q waves after myocardial infarction prompted Prinzmetal et al.[10] to defer their experiments on Q wave genesis for 11 to 139 hours after coronary occlusion.

The work reported here was designed to help explain the delay in appearance of these laboratory indexes of myocardial infarction in relation to the early electron microscopic findings of irreversible damage. In acute experiments, with use of a stop-flow technique and sham-operated controls, coronary sinus and venous enzyme levels and the emergence of significant electrocardiographic Q waves were assessed during and after release of coronary occlusion of 1 to 3 hours' duration. In addition, the preparation permitted study of the indexes of myocardial ischemia: S-T segment elevation in the electrocardiogram, contractility of the myocardium supplied by the occluded vessel, and reactive hyperemia after release of occlusion. The preliminary results have been reported previously.[11]

Methods

Acute experiments were performed in 25 dogs weighing 13 to 21 kg; 20 were subjected to coronary occlusion, and 5 served as sham-operated controls. Each animal was anesthetized with intravenously administered sodium pentobarbital, 30 mg/kg body weight, and placed in the left oblique position. With use of artificial ventilation through a tracheal cannula, the chest was entered by block resection of a portion of the chest wall including the left third, fourth and fifth ribs. As little traumatized tissue as possible was left in the animal so that there would be minimal release of enzymes from injured skeletal muscle into the circulation.

The pericardium was incised and the heart suspended in a pericardial cradle. A segment of the left anterior descending coronary artery was dissected and a snare of thin rubber band was placed around it in 14 dogs including the 5 sham-operated dogs. In 11 experiments the left anterior descending artery was cannulated and perfused from the left carotid artery. In the latter group, blood flow was measured with an electromagnetic flowmeter (Biotronex model BL310) using an extracorporeal flow transducer interposed in the perfusion circuit. A Walton-Brodie strain gauge was sutured to the epicardium to record myocardial contractility of an area supplied by the left anterior descending artery. In this same area, a plunge electrode made of Teflon®-coated stainless steel wire, 0.01 mm in diameter with a 0.5 mm bare tip, was inserted subepicardially to record a unipolar electrocardiogram.

A modified Morawitz cannula was introduced through the left external jugular vein and ligated in the coronary sinus. The coronary sinus blood returned to the right atrium through a cannula inserted into the right external jugular vein. A T tube interposed in the circuit allowed sampling of the coronary sinus blood. A cannulated femoral vein permitted sampling of systemic venous blood and administration of drugs. All animals were given heparin, 10 mg/kg. In later experiments, lidocaine, 20 to 50 μg/kg per min, was infused intravenously for up to 15 minutes immediately after coronary occlusion and release to reduce the incidence of serious ventricular arrhythmias. A femoral artery was cannulated and attached to a Statham transducer (model 23AC) to measure arterial blood pressure.

Recordings were made on a Beckman Dynograph (type R) with two motor drives. Arterial blood pressure, blood flow in the left anterior descending coronary artery and myocardial contractility were recorded continuously at a paper speed of 25 mm/min. On two additional channels, tracings of myocardial contractility and the electrocardiogram were recorded intermittently at a paper speed of 25 mm/sec. Heart rate was measured from the electrocardiogram.

Before operation, a clotted venous blood sample was obtained. After operation, paired samples of coronary sinus and systemic venous blood were drawn at 30 to 60 minute intervals. In 20 animals the left anterior descending artery was occluded for 1 to 3 hours, and then the occlusion was released. Paired blood samples were obtained every 30 to 60 minutes after occlusion, and more frequently after release. In the five sham-operated control animals, paired samples were drawn at hourly intervals after operation. All blood samples were assayed for serum GOT and CPK levels by spectrophotometric methods.[12,13] The coronary sinus and systemic venous enzyme levels were plotted against time in each experiment, and the slope of each curve before release of occlusion was compared with the slope after release, using the analysis for the fitted least-square line.[14]

Reactive hyperemia was recorded after a 1 minute clamping of the perfusion circuit in the animals with coronary blood flow measurements, both before occlusion and 30 to 60 minutes after release. The magnitude of reactive hyperemia was calculated as the peak increase in flow compared with the control value. The magnitude of hyperemia obtained after release of occlusion was compared with that obtained before release in the same animal and expressed as percent reduction. The distance from the left coronary ostium to the point of occlusion of the left anterior descending artery was measured post mortem.

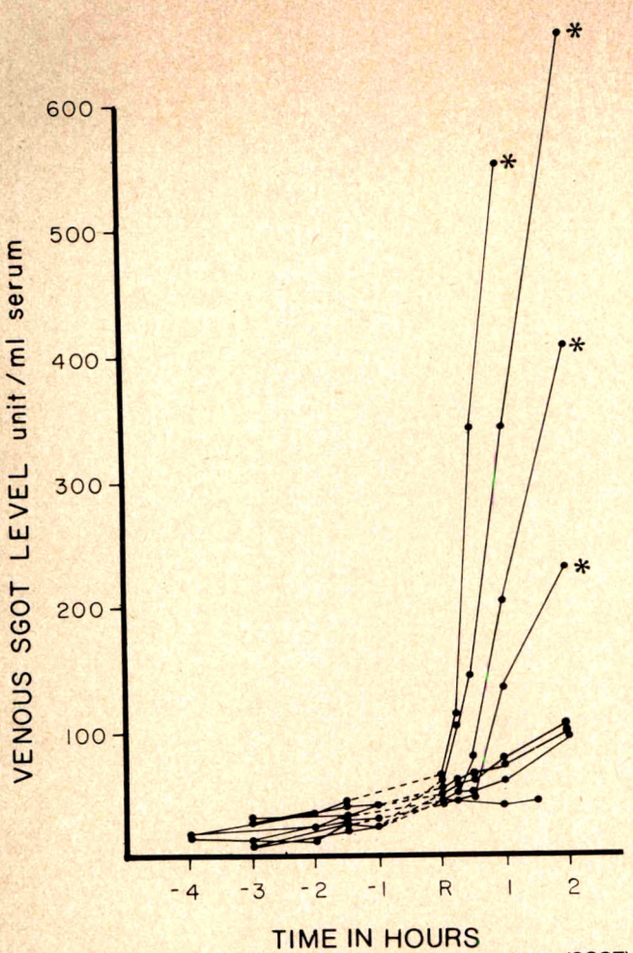

FIGURE 2. Venous serum glutamic oxalocetic transaminase (SGOT) values in international units in eight animals with 1 to 1 1/2 hours of occlusion of the left anterior descending coronary artery. **Broken line** indicates period of occlusion: 1 hour in five experiments and 1 1/2 hours in three experiments. R indicates time of release of occlusion; * indicates significant rise in enzyme levels after release.

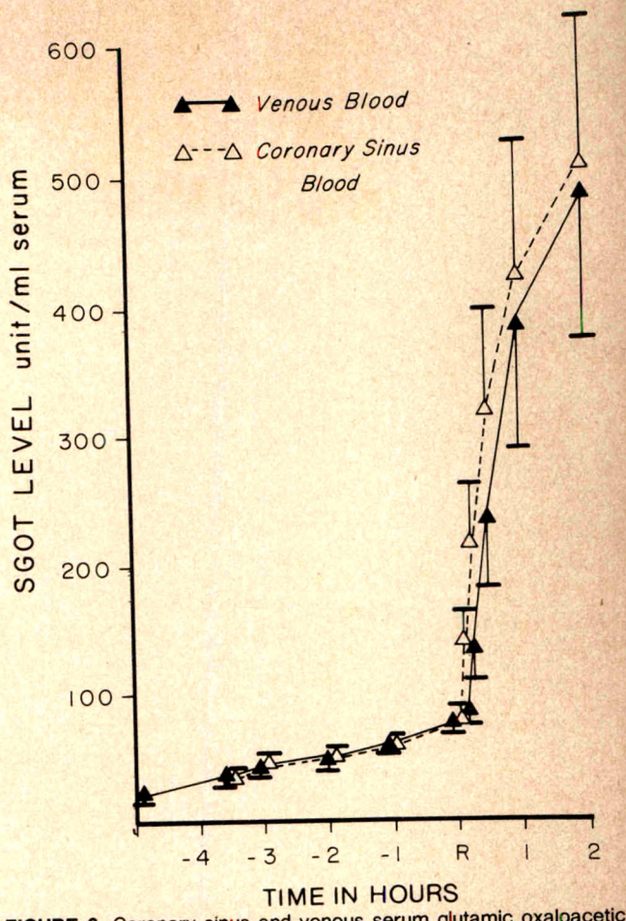

FIGURE 3. Coronary sinus and venous serum glutamic oxaloacetic transaminase (SGOT) levels in 12 animals with 2 to 3 hours of occlusion mean ± standard error of the mean. R indicates time of release of occlusion. Elevation of the coronary sinus SGOT level precedes elevation of venous level by 10 to 20 minutes after release of occlusion.

Results

Twenty animals were successfully brought to the conclusion of the experiment; 8 dogs underwent coronary occlusion for 1 to 1 1/2 hours and 12 dogs for 2 to 3 hours. In addition, five sham-operated dogs were followed up for 6 1/2 hours to serve as controls in the study of elevation of enzyme levels due to the operative procedure.

Serum Enzymes

Sham-operated animals: Figure 1 shows the composite results in five sham-operated animals of serum GOT and CPK determinations in coronary sinus and venous samples. The levels of both enzymes rose gradually to approximately four times control levels in 6 1/2 hours (5 hours after completion of operation). Coronary sinus and venous values were in close agreement at each sampling time. At no period was there an abrupt change in enzyme levels in any of the animals.

Experimental animals: In Figure 2 venous serum GOT values are plotted against time for the eight animals with coronary occlusion of 1 to 1 1/2 hours' duration (five with 1 hour and three with 1 1/2 hours of occlusion). The enzyme levels remained in the range established by the control animals until release of the occlusion. After release, the slope of the curve showed no significant change in four animals (two with 1 hour and two with 1 1/2 hours of occlusion), but increased significantly in the remaining four ($P < 0.05$). Parallel results were obtained for venous CPK values. Coronary enzyme curves also remained in the range of values of the sham-operated dogs until release of occlusion. After release, the same four animals also had significant enzyme increases, but the change in slope preceded the change in venous slope by 10 to 20 minutes as described later for the animals with 2 to 3 hours of occlusion.

Twelve animals had occlusion of the left anterior descending coronary artery for 2 to 3 hours: six for 2 hours, three for 2 1/2 hours and three for 3 hours.

Serum enzyme values remained within the control range before release of occlusion as in the animals with 1 to 1 1/2 hours of occlusion, but the slope of the curve rose significantly after release in all 12 dogs with 2 to 3 hours of occlusion. Mean values and standard error were used to compare coronary sinus and venous enzyme levels at each sampling time (Fig. 3 and 4). Again, there was close agreement between coronary sinus and venous enzyme values before release of occlusion. After release, the coronary sinus level was higher than the venous level at each sampling time, thus confirming the heart as the source of the increase in serum enzymes. However, the time required for the venous level to reach any specific coronary sinus level remained 10 to 20 minutes even after the slope had begun to decrease. These observations pertained for both serum GOT and CPK levels throughout the experiment. The marked individual variations in the magnitude of the enzyme increase after release of occlusion is represented by the large standard error of the mean.

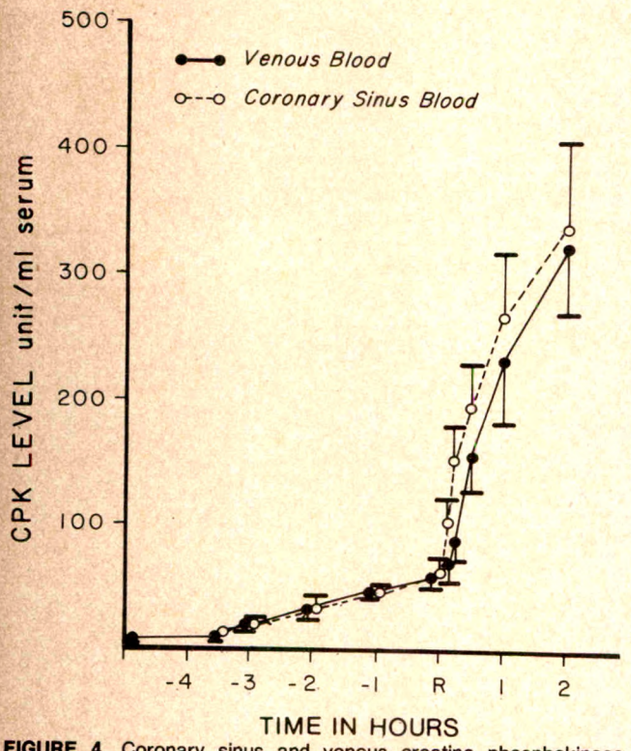

FIGURE 4. Coronary sinus and venous creatine phosphokinase (CPK) levels in the 12 animals whose data are shown in Figure 3. All values are mean ± standard error of the mean. Again, elevation of coronary sinus CPK precedes elevation of venous CPK by 10 to 20 minutes after release (R) of occlusion.

Other measurements: With coronary occlusion, mean arterial blood pressure decreased from an average of 95 to 83 mm Hg, but in none did it fall below 60 mm Hg. Mean heart rate rose from 164 to 177 beats/min. The distance from the left coronary ostium to the site of occlusion of the left anterior descending coronary artery ranged from 1.5 to 3.1 cm. No correlation could be found between any of these variables and the magnitude of enzyme increase in this small series.

Electrocardiogram

The QRS complex and the S-T segment were considered separately in determining electrocardiographic changes. During the experiments, the T waves followed no definite pattern. A Q wave was considered significant if it measured more than 50 percent of the QRS complex. S-T segment elevation of more than 2 mm was considered significant.

QRS complex: In the group with 1 to 1 1/2 hours of occlusion, the four animals with no significant increase in serum enzymes had no significant Q waves. The four animals with a significant increase in serum enzymes all manifested significant Q waves after release of occlusion. Of the 12 animals that underwent 2 to 3 hours of occlusion, 10 had significant Q waves; in the remaining 2, the pattern changed from Rs to rS. Although all 12 of these animals had increased serum enzymes after release of occlusion, the increase was relatively small in the latter two.

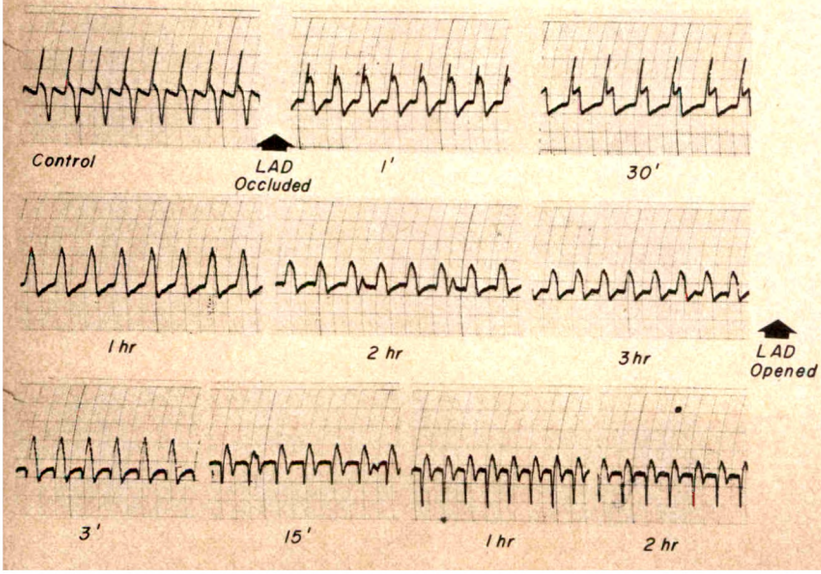

FIGURE 5. Subepicardial electrocardiogram in an animal with 3 hours of occlusion of the left anterior descending coronary artery (LAD). No q wave appeared during the period of occlusion; 3 minutes after release of occlusion (**second arrow**) a q wave appeared and became significant 15 minutes after release. The S-T segment was elevated 7 minutes after occlusion and was still elevated 2 hours after release.

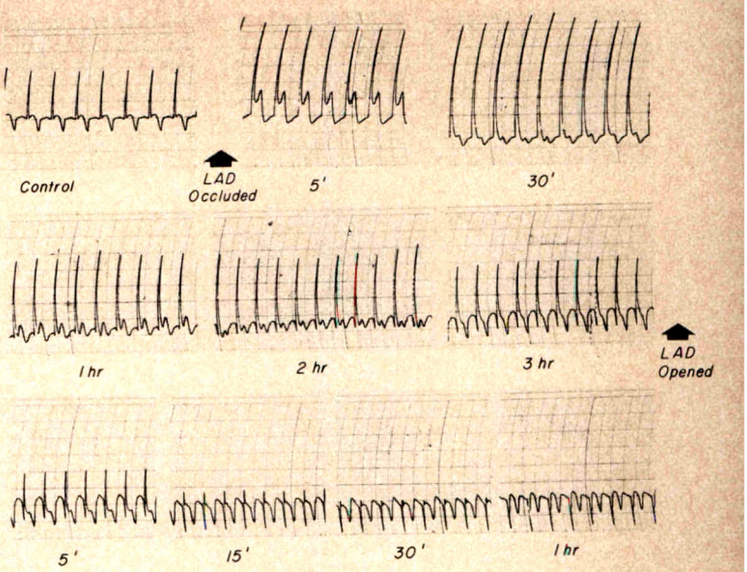

FIGURE 6. Subepicardial electrocardiogram in an animal with 3 hours of occlusion of the left anterior descending coronary artery (LAD). A small q wave developed 1 hour after occlusion; 15 minutes after release (**second arrow**) a significant Q wave was present. The S-T segment was elevated 5 minutes after occlusion, returned to normal in 30 minutes and remained normal for the duration of the experiment.

Thus, significant Q waves were noted in 14 animals, 4 with 1 to 1 1/2 hours and 10 with 2 to 3 hours of occlusion; in all, the electrocardiographic changes developed 15 to 30 minutes after the release of occlusion. Among those with 2 to 3 hours of occlusion, three showed no q wave until after release of occlusion (Fig. 5); in the other seven a small q wave developed during occlusion (Fig. 6 and 7). Surprisingly, the Q waves became significant while serum enzyme levels were rising steeply.

S-T segment: All of the 16 dogs with a significant increase in serum enzymes (4 with 1 to 1 1/2 hours and all 12 with 2 to 3 hours of occlusion) had S-T segment elevation within 2 to 3 minutes after occlusion. The S-T segment remained elevated after release of occlusion in 3 dogs (Fig. 5) and returned to control level during occlusion in 2 dogs (Fig. 6); the dominant pattern, observed in 11 dogs, was a return to control level after release of occlusion (Fig. 7).

In two animals with this dominant pattern, the left anterior descending coronary artery was reoccluded 1 1/2 hours after release of the first occlusion. The S-T segment again became elevated, the Q wave persisted and, on release of occlusion, the S-T segment once again returned to normal (Fig. 7).

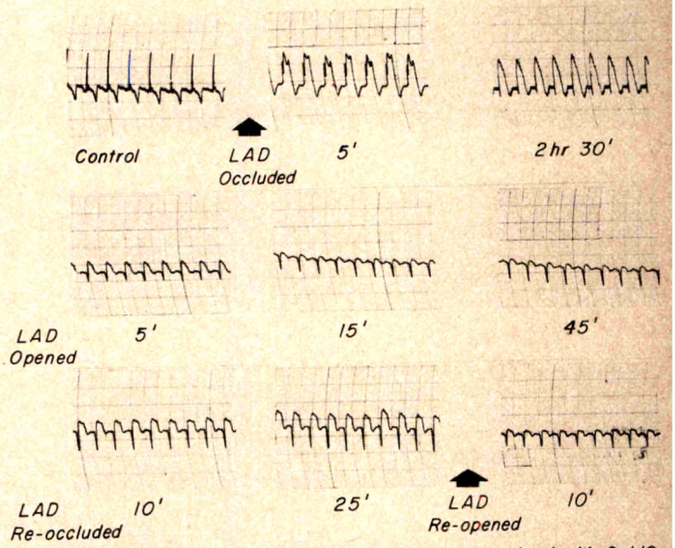

FIGURE 7. Subepicardial electrocardiogram in an animal with 2 1/2 hours of occlusion of the left anterior descending coronary artery (LAD) and reocclusion 1 1/2 hours after release. A small Q wave was present 2 1/2 hours after occlusion and became significant 15 minutes after release. The S-T segment was elevated 5 minutes after occlusion, remained elevated for the duration of occlusion, and returned to normal 15 minutes after release. Ten minutes after reocclusion, the S-T segment again became elevated and the Q wave persisted; 10 minutes after release of this second occlusion, the S-T segment returned to normal.

Myocardial Contractility and Reactive Hyperemia

Myocardial contractility*: Contractility was recorded from the area supplied by the occluded coronary artery in 8 animals with 1 to 1 1/2 hours of occlusion and in 10 with 2 to 3 hours of occlusion. Four of the eight dogs with 1 to 1 1/2 hours of occlusion that had no significant increase in serum enzyme levels had a reduction in contractility of less than 45 percent (range 0 to 44 percent), the same decrement noted in the sham-operated animals. The remaining four dogs in this group had significant serum enzyme increases and a reduction in myocardial contractility of more than 55 percent (range 56 to 77 percent). All 10 dogs with 2 to 3 hours of occlusion also had a reduction in contractility of more than 55 percent (range 56 to 91 percent).

After occlusion, the myocardial contractility tracing characteristically assumed a flat-top appearance as opposed to the sharp spike seen before occlusion

* Myocardial contractility, as recorded with a Walton-Brodie strain gauge, is a measurement of isometric contraction in a stretched segment of epicardium. The recording is affected by the direction of the underlying muscle fibers and the change in shape of the ventricle with contraction, and it does not quantitatively reflect the change in contractility of the entire thickness of the myocardium. The results presented here, comparing recordings obtained before and after occlusion and expressed as percent change, should be interpreted with this reservation.

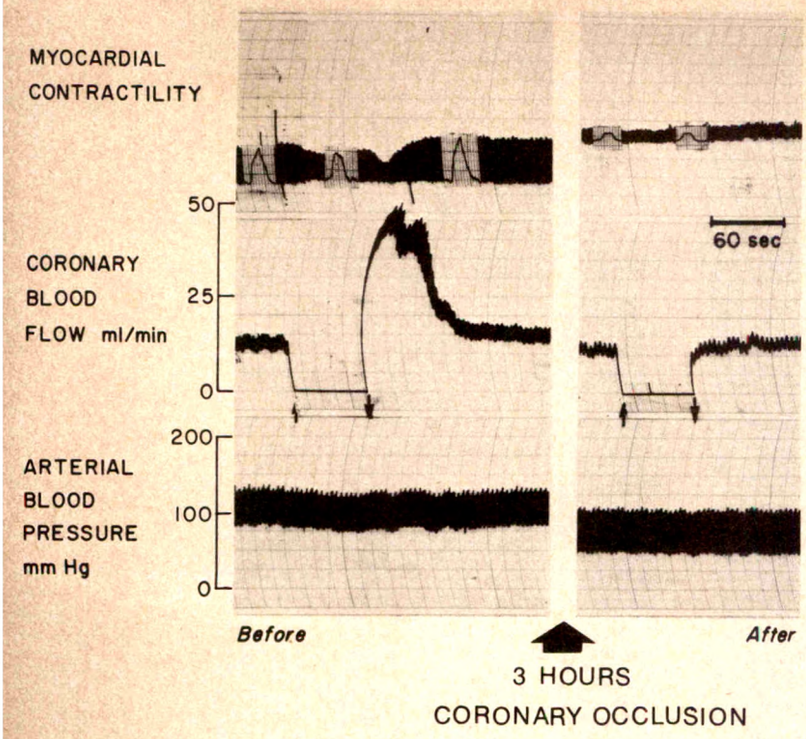

FIGURE 8. Effect of 3 hours of occlusion of the left anterior descending coronary artery on myocardial contractility, reactive hyperemia as shown in the tracing of blood flow in the left anterior descending artery, and arterial blood pressure. **Left panel,** tracing obtained during 1 minute of clamping of the artery before occlusion. **Right panel,** tracing obtained after release of occlusion. Rapid traces of myocardial contractility are superimposed upon the slow tracings. After the 3 hour period of occlusion reactive hyperemia was absent. Myocardial contractility and arterial blood pressure were not affected by the 1 minute period of clamping (**right panel**).

(Fig. 8, top tracing, right panel). Contractility decreased rapidly with occlusion, as illustrated during the 1 minute period of clamping before occlusion in Figure 9, left panel. A temporary increase in contractility was observed after the release of a 1 minute clamping during the control period (left panels, Fig. 8 and 9).

Reactive hyperemia: This variable was measured after 1 minute of clamping in 11 animals before occlusion, and the measurement was repeated 1/2 to 1 hour after the occlusion had been released. Before occlusion, reactive hyperemia peaked at 1.5 to 3.8 times the control rate of blood flow in the left anterior descending artery, and subsided in 2 to 4 minutes. Of three dogs with occlusion for 1 to 1 1/2 hours, two had no rise in serum enzyme levels; one of these had no change in reactive hyperemia and the other only a 12 percent reduction. The third dog had a significant rise in serum enzyme levels and a 29 percent reduction in reactive hyperemia. The eight dogs with 2 to 3 hours of occlusion had a reduction in reactive hyperemia of 35 to 100 percent (mean 67 percent).

Figures 8 and 9 illustrate, for two experiments, the changes in reactive hyperemia, myocardial contractility and arterial blood pressure associated with 1 minute of clamping before and after a 3 hour occlusion of the left anterior descending coronary artery. Figure 8 shows a complete loss of reactive hyperemia after occlusion and a 75 percent reduction in myocardial contractility (right panel). Arterial blood pressure values were not affected by the 1 minute of clamping after occlusion compared with the slight reduction in values before occlusion (left panel). In another animal (Fig. 9, right panel), reactive hyperemia was reduced by only 35 percent. This retained capacity for reactive hyperemia was associated with a slight decrease in myocardial contractility during clamping and a temporary increase on release, as well as a slight reduction in arterial blood pressure during clamping. These changes were much smaller than those that occurred before occlusion (left panel), but are indicative of remaining myocardial function in the infarcted area after occlusion and are in contrast to the findings illustrated in Figure 8 (right panel).

Discussion

Coronary occlusion leads to myocardial ischemia and thence to myocardial infarction. In the experiments reported here, the presence of myocardial infarction was suggested by an abrupt rise in serum enzyme levels and a rapid development of significant electrocardiographic Q waves after release of occlusion. These findings occurred in some animals even after occlusion of only 1 hour's duration. Ancillary evidence of infarction included loss of myocardial contractility and reduced reactive hyperemia. Residual viable muscle in the infarcted area was assumed to be present when (1) reocclusion caused elevation of the S-T segment in the electrocardiogram, (2) some return of myocardial contractility followed release of occlusion, and (3) some capacity for reactive hyperemia was retained after release of occlusion.

Serum Enzymes

The sham-operated control animals manifested a range of elevation of serum enzyme levels caused by the operative procedure alone. These values are in agreement with previously reported observations.[15]

In the animals that underwent coronary arterial occlusion and release, three pertinent observations emerged. First, in every dog that underwent 2 to 3 hours of coronary occlusion, elevated serum enzyme

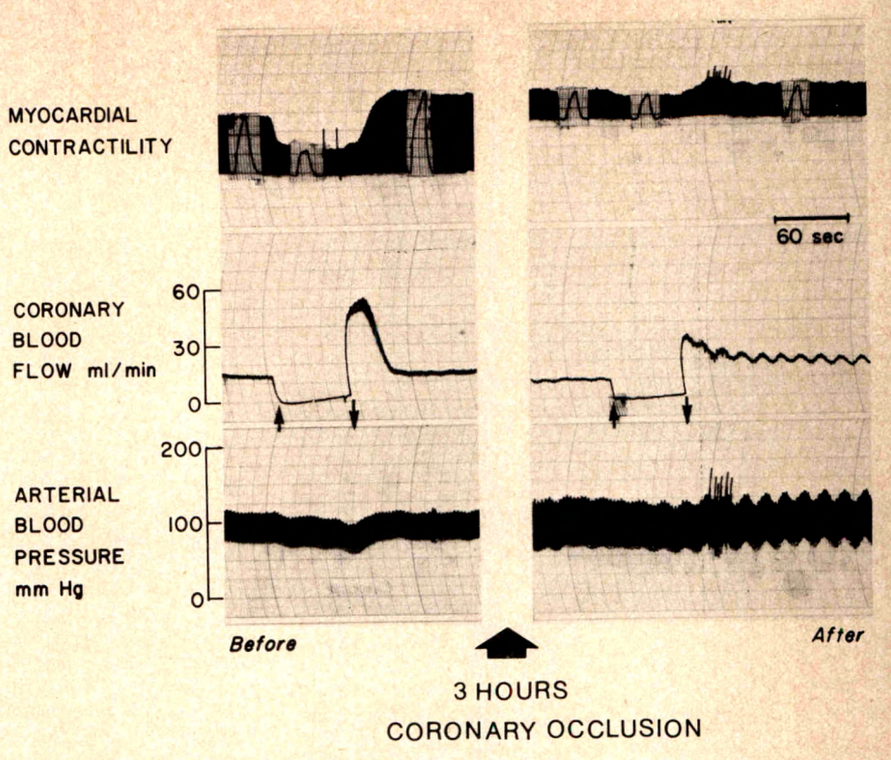

FIGURE 9. Effect of another 3 hour occlusion experiment. Records as in Figure 8. After 3 hours of occlusion, some capacity for reactive hyperemia was retained, associated with some loss of myocardial contractility and a slight reduction in arterial blood pressure during the 1 minute clamping period (**right panel**).

levels occurred almost immediately after release of occlusion (Fig. 3 and 4); serum enzymes were increased in some dogs that underwent 1 to 1 1/2 hours of occlusion but not in others (Fig. 2). Second, restoration of circulation to the infarcted area was responsible for the abrupt rise in enzyme levels; the myocardium was the source of this rise since elevation of enzyme levels in coronary sinus blood preceded that in venous blood. Third, venous enzyme elevation after release of occlusion lagged only 10 to 20 minutes behind the enzyme elevation in coronary sinus blood; this lag was apparent immediately on release of occlusion and remained fairly constant even as the rate of rise began to decrease 1 to 2 hours after release. On the basis of these observations, the time from coronary occlusion to the appearance of elevated venous enzyme levels can be divided into three periods for the purpose of discussion: the *viable period,* when heart muscle cells may still recover if circulation is restored; the *stagnant period,* when the cells are irreversibly damaged but there is insufficient circulation to remove the enzymes; and the *lag period* between the rise of enzyme levels in the coronary sinus blood and enzyme elevation in venous blood.

Viable period: Our data on serum enzyme levels suggest, on first inspection, that the *viable period* lasts less than 2 hours since all animals with occlusion of 2 hours or more had increased serum enzymes after release (Fig. 3 and 4). Indeed, the increase in serum GOT after release of a 1 hour occlusion in three animals (Fig. 2) closely corroborates the electron microscopic data derived from papillary muscle having no collateral circulation and showing irreversible damage after 40 to 60 minutes of occlusion.[2] However, four of our animals with 1 to 1 1/2 hours of occlusion had no significant increase in serum GOT after release, and therefore probably sustained no irreversible myocardial damage. Moreover, there were wide individual variations in the degree of enzyme elevation after release of 2 to 3 hours of occlusion, illustrated by the large standard error of the mean in Figures 3 and 4. This variation did not correlate with the distance from the coronary ostium to the point of occlusion. Some other mechanism or mechanisms must pertain. Prinzmetal[10] and Maxwell[16] and their coworkers described two types of experimental myocardial infarction on the basis of pathologic changes: transmural and patchy. Their two types of myocardial infarction and our variations in enzyme increase may both be attributable to the degree of existing collateral circulation before coronary occlusion. This concept is supported by the observation that drugs that affect collateral vessels influence infarct size.[17] Moreover, it has been shown that smaller infarcts and higher survival rates are found when additional collateral circulation is stimulated by coronary arterial constriction before ligation.[18] In this context, the short, viable period observed electron microscopically in posterior papillary muscle may be related to the known absence of collateral circulation to this area, whereas the more variable and generally longer viable period in our experiments may be a result of existing collateral circulation. Interestingly, the relatively rich collateral circulation of the dog heart has been likened to that in the human heart with coronary artery disease.

Stagnant period: This period, so-called because of poor circulation in the infarcted area, was abridged in our experiments by reperfusion. Ample support for a relatively long clinical *stagnant period* is afforded by reports of other investigators. For example, heart muscle loss of GOT does not begin until 4 hours after

occlusion and only 40 to 50 percent of the enzyme is lost in 24 hours.[3,9] In fact, even 24 hours after coronary occlusion, the circulation in the infarcted area is only 12 percent of that in the noninfarcted myocardium as measured by injection of microspheres.[19] The truth is that enzymes cannot be removed if there is no circulation to remove them. However, other factors also influence the speed of removal of enzymes from infarcted myocardium. The anatomy of the infarct is relevant since elevated serum enzyme levels appear sooner than usual after microinfarcts produced by bead embolization.[7,8] Another factor is molecular weight, since enzymes of lower molecular weight became increased in the serum before those of higher molecular weight.[20] Most interesting of all is the observation that reperfusion 40 to 60 minutes after occlusion causes more rapid destruction of sarcolemmal membranes and extrusion of intracellular contents[21] although reperfusion *per se* actually decreases infarct size.[22] Nonetheless, in our experiments, the more rapid destruction of sarcolemmal membrane of irreversibly damaged cells could have contributed to the abrupt rise in coronary sinus and then venous enzyme levels.

Lag period: The time required for the venous enzyme level to reach a specific coronary sinus enzyme level defines the *lag period.* Of the three periods, this one is best illustrated by the experiments reported herein. The lag period is shown in Figures 3 and 4 as the distance along the abscissa from the coronary sinus curve to the venous curve after release of occlusion. With recognition of the assumptions of constant coronary blood flow and blood volume, and the need for corrections for mixing time and half-life of enzymes, it can be expressed as follows:

$$\text{Lag period (min)} = \frac{\text{Blood volume (ml)}}{\text{Coronary blood flow (ml/min)}}$$

Substituting standard values supports the gross applicability of this formula to the experimental findings. Especially relevant in the mathematical derivation is the fact that a slow rise or fall in the rate of enzyme leaving the infarcted myocardium does not greatly affect this approximation.* For example, a 20 percent decrease during one lag period (approximately 20 minutes) would prolong the lag by 10 percent or 2 minutes. Thus, this conception of a relatively short lag period is applicable to myocardial infarction in man. In effect, venous enzyme elevation detected clinically presumably lags only minutes behind coronary sinus levels. This relationship can be adapted to other organ effluents monitored by peripheral venous sampling provided that the necessary assumptions and corrections are acceptable: the lag period varies inversely with the organ blood flow and directly with the fluid volume into which the substance mixes.

* When the rate of release of enzyme (E) from the infarcted myocardium is changing slowly, and the change during one lag period is represented by ΔE, the following formula pertains:

$$\text{Lag (min)} \approx \frac{\text{Blood volume (ml)}}{\text{Coronary blood flow (ml/min)}} \cdot \left(1 - \frac{1/2\ \Delta E}{E}\right)$$

Electrocardiogram

Q waves became significant within 30 minutes after release of occlusion in 14 of 16 animals with serum enzyme elevations. Clinically, Q waves are delayed at least as long as required for elevation of serum enzyme levels. The telescoping of Q wave formation in our experiments parallels the washout of enzymes after release of occlusion. One possibility suggested by this correlation is that removal of one or more substances allows the emergence of cavity potential. However, it is possible that preservation of the sarcolemmal membranes in the early periods of myocardial infarction[21] delays appearance of the Q wave. With reperfusion, disruption of these membranes might alter the electrophysiologic properties of the cells in a way that could accelerate Q wave emergence. The precise explanation awaits further studies. Nevertheless, at this juncture it seems reasonable to conclude that the delay in Q wave appearance in clinical myocardial infarction is a result of the compromised perfusion of the infarcted area and does not imply a prolonged period during which death of heart muscle slowly occurs.

S-T segment shift: Alteration in the S-T segment represents a prompt and reversible response to myocardial ischemia.[23] S-T elevation recorded on multiple epicardial electrocardiograms has been used to map the ischemic area shortly after coronary occlusion.[17] In our experiments, with only one subepicardial recording near the center of the ischemic area, the S-T segment rose promptly after coronary occlusion. In the majority of experiments, the S-T segment manifested persistent elevation throughout occlusion and returned to normal with reperfusion. This pattern, which suggests subsidence of ischemia in remaining viable myocardial cells, occurred despite the concomitant appearance of Q waves. In two experiments (one shown in Fig. 7), 1 1/2 hours after release of occlusion, the left anterior descending artery was reoccluded, and the S-T segment again became elevated while the Q wave remained; the S-T segment returned to normal on release of this second occlusion. We conclude that in these experiments the infarcted area contained viable myocardial cells as well as cells with irreversible damage. The implication for myocardial infarction without reperfusion is that either these cells survive, forming patchy infarction, or that they eventually succumb.

Myocardial Contractility and Reactive Hyperemia

Myocardial contractility decreases very promptly upon occlusion of a coronary artery, demonstrating an even more rapid response to myocardial ischemia than that of S-T elevation and occurring long before either index of infarction develops. In some of our experiments, no recovery of contractility appeared after release of occlusion (Fig. 8), and this finding implies that transmural infarction had occurred. In others, some return of contractility was apparent (Fig. 9), indicating patchy infarction with areas of viable muscle that resumed contraction when circulation was re-

stored. These observations are consistent with results of cineradiographic studies in coronary arterial reperfusion experiments.[24] They further corroborate the observation that an asynergic area revealed by ventriculography in man does not exclude the presence of viable ischemic myocardium.[25]

Reactive hyperemia represents one or more vasodilating mechanisms in viable ischemic muscle that affect the vascular bed. In our experiments, the magnitude of reactive hyperemia correlated with the return of myocardial contractility. Moreover, it was a more reliably measured index of salvageable or salvaged ischemic myocardium after coronary occlusion. Indeed, diastolic reactive hyperemia is being used to evaluate the benefit derived from coronary artery bypass operations.[26]

Clinical Implications

In selecting patients for coronary artery bypass surgery, the *sine qua non* is the demonstration of an operable lesion by angiography. Our data pertain to further selection of patients after myocardial infarction and to postoperative evaluation.

The usual clinical indicators of acute myocardial infarction, a rise in venous enzyme levels and significant electrocardiographic Q waves, do not obtain during the first few hours after coronary occlusion. Indeed, after coronary artery bypass surgery for acute myocardial infarction, increase in serum enzyme levels and progressive development of a Q wave may represent the natural course of reperfusion rather than damage resulting from operation. Before and after operation, the venous enzyme level reliably reflects the coronary sinus enzyme level minutes later.

During the postinfarction period, S-T segment deviation identifies ischemic myocardium even in the presence of Q waves. The use of grid electrocardiography for this determination has already been reported.[17]

After operation, the value of measurement of reactive hyperemia in the bypass graft to assess the effectiveness of the procedure is supported by our data. These results should correlate with myocardial contractility demonstrated by ventriculography.

Acknowledgment

We thank Mr. Philip Goad for his technical assistance and Dr. Martin Kruskal, professor of astrophysical sciences and applied mathematics, Princeton University, for his aid in explaining the lag between coronary sinus and venous enzyme levels after release of coronary occlusion.

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Alterations in Energy Metabolism and Ultrastructure Upon Reperfusion of the Ischemic Myocardium After Coronary Occlusion

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The effects on myocardial function, metabolism and ultrastructure of 60 minutes of reperfusion, instituted after 30, 60 and 90 minutes of occlusion of the left anterior descending coronary artery, were studied in 48 dogs. Twelve sham-operated dogs served as controls. Coronary occlusion for 60 or 90 minutes caused significant depression in the first derivative of left ventricular pressure (dP/dt) ($P < 0.05$) that could not be reversed by reperfusion. Upon reperfusion, creatine phosphate stores in myocardium made ischemic for 30 and 60 minutes, but not for 90 minutes, returned toward control levels, but stores of adenosine triphosphate (ATP) and total nucleotides and the ATP/adenosine diphosphate ratio of myocardium subjected to 60 and 90 minutes of ischemia were further decreased. After 60 and 90 minutes of ischemia, swelling of the sarcoplasmic reticulum and mitochondrial damage (swelling, decreased matrix density and partial loss of cristae) were seen. Myofibrils were relaxed in all these groups. Reperfusion produced gross contraction of myofibrils and aggravated these changes in mitochondria and sarcoplasmic reticulum. In the hearts subjected to 90 minutes of ischemia these changes were gross. The levels of creatine phosphokinase, glutamic oxaloacetic transaminase and lactic dehydrogenase in the coronary sinus blood increased dramatically ($P < 0.05$) upon reperfusion after 60 or 90 minutes of occlusion, indicating severe impairment of cell membranes. This secondary rise in serum enzyme activity during reperfusion should be taken into consideration when estimating the size of a myocardial infarct from enzyme changes alone. It appears that 60 and 90 minutes of ischemia cause severe myocardial damage that is not reversed by reperfusion maintained for 1 hour although longer periods of reperfusion may be beneficial.

Although ischemia produced by coronary occlusion has repeatedly been demonstrated to produce dramatic changes in myocardial function, ultrastructure and metabolism, there are only a few reports concerning the effects of reperfusion on the ischemic myocardium. Such information is considered of crucial importance in determining the timing and feasibility of coronary bypass surgery in patients with myocardial infarction. Recently, deterioration of the contractile activity of the ischemic zone upon institution of reperfusion after 1 to 2 hours of occlusion has been reported.[1] In this paper we demonstrate that irreversibility of ischemic myocardial function upon reperfusion after 1 to 2 hours of coronary occlusion is associated with dramatic changes in myocardial metabolism, ultrastructure and enzyme leakage.

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Methods

Sixty healthy mongrel dogs, of either sex and an average weight of 30.9 ± 5.8 (mean ± standard error of the mean) kg body weight, were used in these experiments. After anesthesia induced with sodium pentobarbital, 20 mg/kg intravenously, the animals were intubated and controlled positive pressure respiration was instituted with use of a Harvard respirator pump. Tidal volume was adjusted to individual body weight (Kleinman-Radford tables) and the animals breathed an air-oxygen mixture with an inspiration/respiration ratio of 45:55. These variables were reviewed and readjusted periodically so as to maintain a stable level of arterial partial pressure of oxygen and pH. In the entire series PO_2 was maintained between 93 and 152 mm Hg (mean 117 ± 21.9) and pH between 7.3 and 7.4 (mean 7.379 ± 0.037). Bilateral femoral cutdown procedures were performed and catheters placed for continuous monitoring of central venous pressure, central arterial pressure, left atrial pressure and left ventricular pressure and its first derivative (dP/dt).

Lateral thoracotomy through the fourth intercostal space was employed to expose the heart. The pericardium was incised 1 cm anterior to the phrenic nerve. The left anterior descending coronary artery was dissected for about 1 cm just distal to the origin of its first major perforating septal branch. A loop of fine Dacron® tape was used to compress the artery against a soft rubber tube so as to cause occlusion without kinking. Visible collateral vessels from the circumflex coronary arterial system entering this zone were transfixed with 2-0 silk ligature. This produced a clearly demarcated area of acute ischemia corresponding to the distribution of the left anterior descending coronary artery distal to the occlusion. In the sham-operated control group, the left anterior descending coronary artery was dissected and looped but not occluded. An exploring electrode was used to detect the center of the infarct, which was the area of most severe change in epicardial electrograms within the cyanotic ischemic area. Electrodes were then placed in the center as well as at the margin of the ischemic zone and over the normal left ventricular wall to monitor the surface electrocardiogram continuously.

Protocol

In 16 animals occlusion of the left anterior descending coronary artery was maintained for 30 (no. = 4), 60 (no. = 6) and 90 (no. = 6) minutes after which a whole thickness tissue biopsy specimen was obtained from the ischemic area for electron microscopic studies with use of a no. 10 Silverman needle. A large punch biopsy specimen (about 10 g of tissue) of the whole thickness of myocardial wall from the ischemic zone was then obtained, using a special instrument that had been precooled in liquid nitrogen, for subsequent homogenization and biochemical analysis.

In an identical group of 16 experiments, myocardial ischemia was maintained for 30 (no. = 4), 60 (no. = 6) and 90 (no. = 6) minutes, and at the end of this period a biopsy specimen from the ischemic zone was obtained for electron microscopic studies. The coronary occlusion was then released and a 1 hour period of reperfusion of the ischemic zone permitted. At the end of this period another biopsy specimen for electron microscopic study was taken and a final punch biopsy specimen for biochemical analysis was obtained as previously outlined.

In a third group of 16 experiments, myocardial ischemia for 30 (no. = 4), 60 (no. = 6) and 90 (no. = 6) minutes was followed by a 1 hour period of reperfusion. A polyethylene

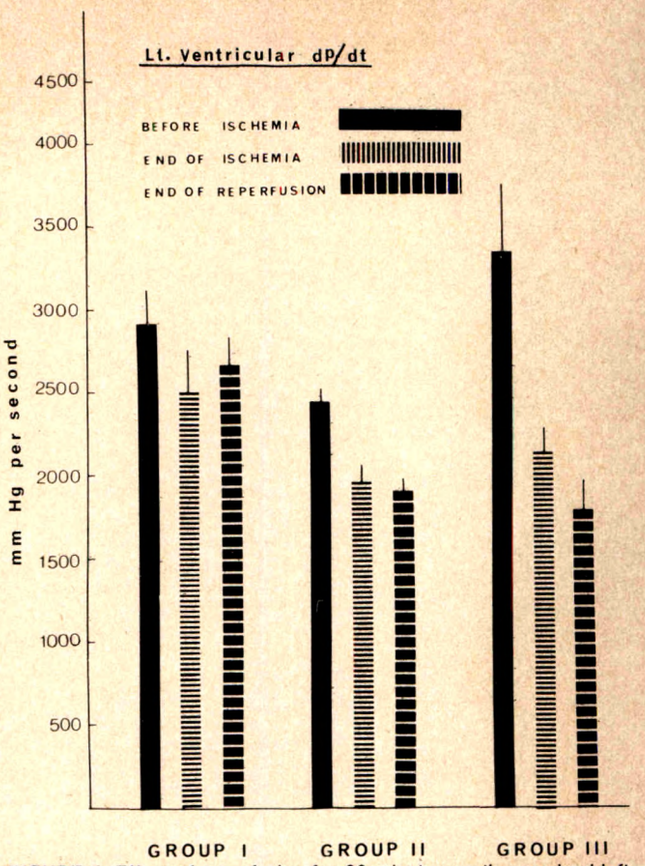

FIGURE 1. Effect of reperfusion for 60 minutes on the maximal left ventricular dP/dt of the ischemic dog myocardium. Groups I, II and III refer to animals with 30 (no. = 4), 60 (no. = 6) and 90 (no. = 6) minutes of coronary occlusion, respectively. Each bar represents the mean ± standard error of the mean. Lt. = left.

catheter (internal diameter 2 mm) was passed by way of the right jugular vein and positioned in the main body of the coronary sinus for obtaining blood samples. In this group the myocardial surface electrogram, central venous pressure, arterial pressure and left ventricular dP/dt were monitored continuously. Blood samples from the coronary sinus were obtained for assessing serum creatine phosphokinase (CPK), glutamic oxaloacetic transaminase (GOT), lactic dehydrogenase (LDH) and blood lactates. Samples for biochemical studies, as well as myocardial tissue biopsy specimens for electron microscopic study, were obtained (1) before occlusion of the left anterior descending coronary artery, (2) at the end of the period of ischemia and (3) at the end of 60 minutes of reperfusion following the release of coronary occlusion. This protocol provided a correlative study of myocardial performance (left ventricular dP/dt), coronary sinus serum enzymes (CPK, SGOT, LDH), myocardial energy metabolism and myocardial ultrastructure before, during and after myocardial ischemia.

For the study of myocardial ultrastructure the tissue was immediately immersed in a solution of 5 percent glutaraldehyde in 0.1 molar phosphate buffer (pH 7.4) and allowed to fix for 1 hour. It was further fixed in buffered 1 percent osmium tetroxide for 1 hour, then dehydrated in graded ethanol series and embedded in Epon 812. Sections were made with a Sorval MT-II Porter-Blum Ultra-microtome using a diamond knife. Sections were stained for 30 minutes using 6 percent uranyl acetate in 70 percent methanol and post-stained with Reynold's lead citrate for 15

TABLE I

Effects of 60 Minutes of Reperfusion on Activity of Cardiac Enzymes in Coronary Sinus Blood (mean ± standard error of the mean)

	Serum Enzymes		
	CPK (mU/ml)	GOT (IU/liter)	LDH (IU/liter)
Group I			
Control value	234.33 ±43.45	49.00 ±6.12	284.67 ±38.35
End of 30 minutes of ischemia	488.33 ±36.92	56.00 ±8.24	170.33 ±35.65
End of 60 minutes of reperfusion	979.67 ±115.13	106.67 ±28.11	194.67 ±56.60
Group II			
Control value	317.00 ±25.78	87.67 ±7.17	169.33 ±17.45
End of 60 minutes of ischemia	498.67 ±17.30	105.33 ±6.45	155.50 ±8.83
End of 60 minutes of reperfusion	3148.50 ±346.66	1538.00 ±277.78	832.75 ±224.24
Group III			
Control value	620.00 ±139.63	95.50 ±10.28	150.33 ±26.70
End of 90 minutes of ischemia	1240.17 ±188.04	134.83 ±16.78	147.00 ±17.86
End of 60 minutes of reperfusion	2645.17 ±363.27	562.67 ±137.43	653.50 ±134.82

CPK = creatine phosphokinase; LDH = lactic dehydrogenase; GOT = glutamic oxaloacetic transaminase.

minutes. Sections were observed on a Zeiss EM9S electron microscope.

High energy phosphates were measured in tissue frozen in liquid nitrogen as follows: A sample weighing 0.5 to 0.7 g was pulverized in liquid nitrogen to a fine powder. Ten volumes of 0.6 N $HClO_4$ was added with stirring. The mixture was allowed to thaw and then centrifuged at 5° C temperature and 2,000 to 3,000 × *g* for 10 minutes. The supernatant was decanted into a precooled beaker in an ice dish and neutralized using 3 molar K_2CO_3. It was further centrifuged as before and the supernatant decanted once again. This protein-free extract was used for measuring creatine phosphate (CP), and adenosine triphosphate (ATP), diphosphate (ADP) and monophosphate (AMP) by enzymatic determination technique.[2] Serum CPK was measured by the technique of Rosalki[3] using an ICN single vial reagent kit and Gilford spectrophotometer. Serum GOT and LDH were measured by automated procedure (Technicon SMA-12/60 system) based upon the technique of Levine and Hill[4] and Morgenstern et al.[5] Lactates were measured by enzymatic determination[6] using Unicam Instruments (SP 500-2 Series) spectrophotometer and BMC test combination reagent kits.

Results

Left Ventricular Performance

The effect of 60 minutes of reperfusion on left ventricular dP/dt was studied in dogs after 30, 60 and 90 minutes of coronary occlusion (Fig. 1). Neither 30 minutes of ischemia nor subsequent reperfusion affected dP/dt values. However, these values were significantly depressed ($P < 0.05$) after 60 or 90 minutes of ischemia and did not show improvement upon reperfusion.

TABLE II

Effect of 60 Minutes of Reperfusion on High Energy Phosphates (mean ± standard error of the mean)

	ATP (μmole/g wet tissue weight)	ATP + ADP + AMP (μmole/g wet tissue weight)
Sham control	5.03 ±0.29	5.94 ±0.32
Group I		
End of 30 minutes of ischemia	4.25 ±0.53	5.57 ±0.50
End of 60 minutes of reperfusion	6.92 ±0.79	7.67 ±0.78
Group II		
End of 60 minutes of ischemia	3.13 ±0.73	4.29 ±0.76
End of 60 minutes of reperfusion	1.84 ±0.10	2.38 ±0.10
Group III		
End of 90 minutes of ischemia	2.41 ±0.16	3.36 ±0.21
End of 60 minutes of reperfusion	1.58 ±0.16	2.03 ±0.18

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate.

Coronary Sinus Serum Enzymes

Coronary occlusion for 30, 60 or 90 minutes slightly (but not significantly, $P > 0.05$) increased CPK and GOT activity levels in coronary sinus blood (Table I). LDH activity did not change significantly ($P > 0.2$).

Upon reperfusion, serum activity levels of CPK, GOT and LDH in coronary sinus blood did not rise significantly ($P > 0.05$) in the group with 30 minutes of ischemia. By contrast, a dramatic increase in the activity of these enzymes was noted upon reperfusion after 60 or 90 minutes of ischemia ($P < 0.05$).

High Energy Phosphate

Coronary occlusion for 30, 60 and 90 minutes decreased ($P < 0.05$) the creatine phosphate content of the left ventricular muscle (Fig. 2). Sixty minutes of reperfusion of myocardium made ischemic for 30 or 60 minutes resulted in partial return to normal creatine phosphate levels ($P > 0.05$); however, no change was seen upon reperfusion after 90 minutes of ischemia. There was a progressive decrease in myocardial adenosine triphosphate, total nucleotides (Table II) and the ratio of adenosine triphosphate to adenosine diphosphate (Fig. 3) after 30, 60 and 90 minutes of coronary occlusion. These variables returned to a level slightly higher than their respective control values upon reperfusion after 30 minutes of myocardial ischemia but were further reduced upon reperfusion after 60 or 90 minutes of ischemia ($P < 0.05$).

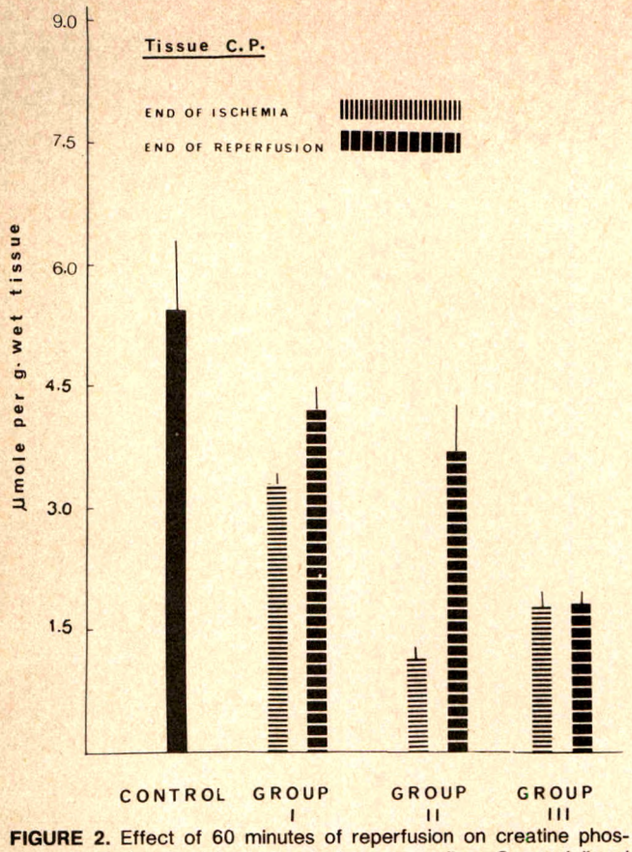

FIGURE 2. Effect of 60 minutes of reperfusion on creatine phosphate (C. P.) levels of the ischemic dog myocardium. Groups I, II and III as defined in Figure 1.

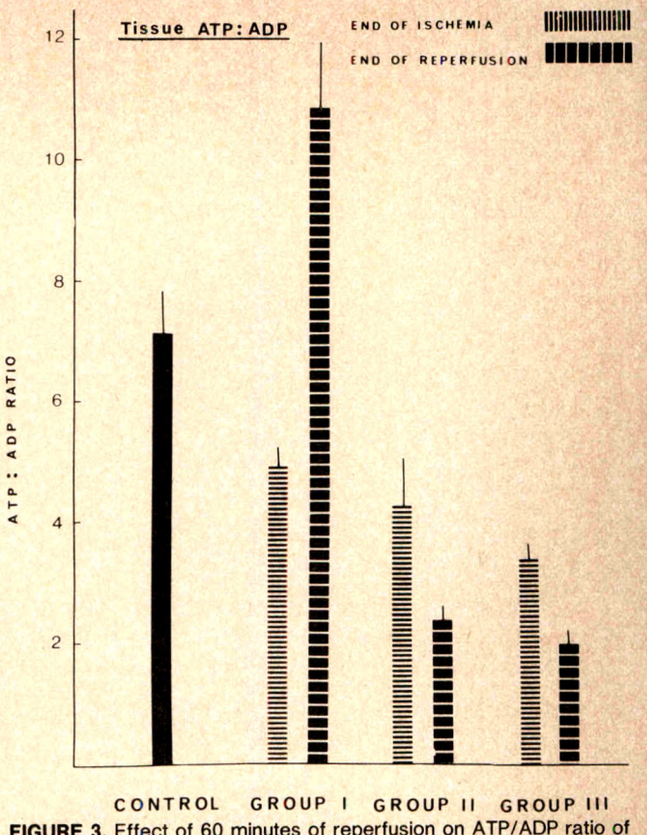

FIGURE 3. Effect of 60 minutes of reperfusion on ATP/ADP ratio of the ischemic dog myocardium. Groups I, II and III as defined in Figure 1.

Ultrastructure

Sections of the left ventricular myocardium subjected to 30 minutes of ischemia revealed that myocardial ultrastructure (Fig. 4A) was not apparently different from that of the sham-operated control heart. The muscle was in a relaxed stage and mitochondria were packed with cristae. However, reperfusion for 60 minutes of myocardium subjected to 30 minutes of ischemia resulted in contracted myofibrils (Fig. 4B).

Although 60 minutes of ischemia resulted in various degrees of damage to the mitochondrial ultrastructure and swelling of sarcoplasmic reticulum (Fig. 5A), the muscle was in a relaxed state. However, mitochondria were markedly swollen, and myofibrils were contracted upon reperfusion after 60 minutes of ischemia (Fig. 5B). Examination of sections obtained from myocardium made ischemic for 90 minutes revealed marked swelling of mitochondria and damage to cristae (Fig. 6A), whereas these muscles after reperfusion showed areas of disrupted myofibrils and extensive mitochondrial damage (Fig. 6B).

Discussion

The aim of the study was to correlate myocardial performance, ultrastructure and biochemical measurements during a period of acute ischemia and to study the effect of reperfusion in reversing any deleterious effects of ischemia on these variables. It was also intended that these correlates be studied in the same hearts as far as possible. The investigations involving myocardial performance, electrophysiology, coronary sinus biochemistry and biopsy studies for electron microscopy can all be performed in the same hearts but an open chest preparation is needed to obtain a biopsy specimen at the end of the ischemic period, which is almost at the middle of the experiment. An open chest preparation was therefore adopted in spite of the known superiority of the closed chest preparation advocated by Corday et al.[7] Every precaution was taken to keep respiratory and hemodynamic variables as stable as possible, as reflected by the stable blood PO_2 and pH values as well as the values of maximal left ventricular dP/dt reported in this series.

Almost all animals had transient cardiac arrhythmias 4 to 8 minutes after the coronary arterial occlusion but in most cases these arrhythmias disappeared spontaneously. The four animals in which the arrhythmias did not disappear spontaneously are not included in this study. Arrhythmias during the period of reperfusion were more severe and persistent. The critical period was between 8 and 20 minutes after the start of reperfusion. Animals that survived this period showed stable cardiac rhythm thereafter and completed the study. In 19 animals, ventricular fibrillation ensued, resulting in a 37 percent mortali-

ty rate due to postperfusion arrhythmias in 51 experiments. These animals are not included in our study because the variable periods of arrhythmia, associated hypotension and direct effect of direct-current countershock, if attempted, would have invalidated the serum enzyme data[8] and to some extent the ultrastructural findings. Thirty-two complete studies were carried out in the remaining animals and are reported here. The series is selective to this extent but has the advantage of being uniform in the course of events, and the values presented show a true relation to each other. Except for the study of high energy phosphates, which required a terminal biopsy specimen, all values presented belong to the same animals.

Myocardial function after reperfusion: Significant deterioration in cardiac function has been re-

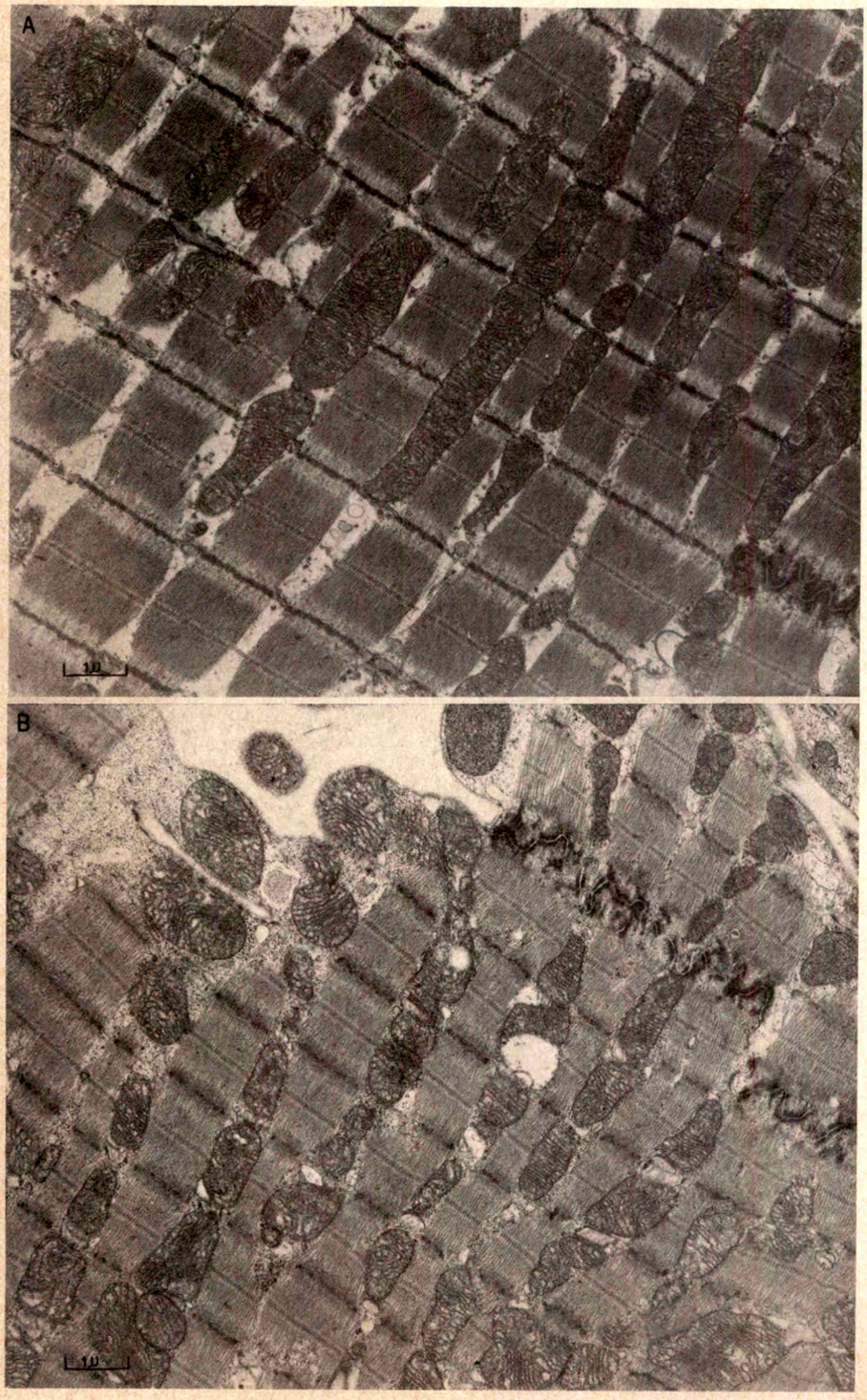

FIGURE 4. Left ventricular cardiac muscle after 30 minutes of coronary occlusion **(A)**, followed by 60 minutes of reperfusion **(B)**. (×16,500, reduced by 50 percent.)

ported by Meerbaum et al.[9] 5 to 30 minutes after occlusion of the left anterior descending coronary artery in a closed chest experimental preparation. Our data in open chest animals are in agreement with this finding but also demonstrate that the reduced maximal left ventricular dP/dt of myocardium made ischemic for 60 to 90 minutes does not increase after 60 minutes of reperfusion. The irreversibility of depressed myocardial contractility upon reperfusion after 1 to 2 hours of coronary occlusion has also been demonstrated by other investigators.[1,10–12] This inability of left ventricular performance to recover upon reperfusion after 60 to 90 minutes of ischemia may be due to a reduced energy state[13] and damaged ultrastructure of the myocardium.[14] Whatever the mechanism of the irreversible damage to ischemic

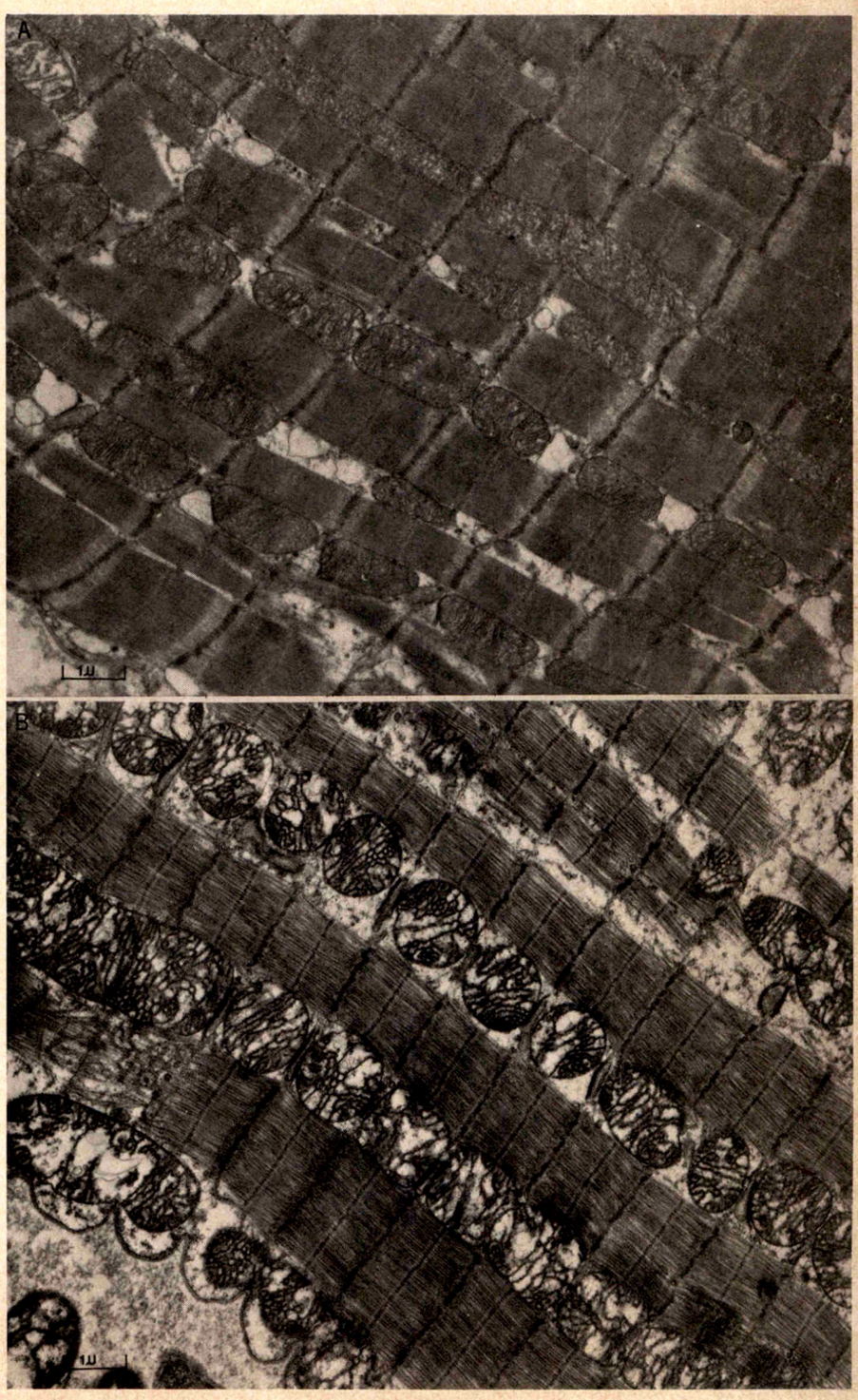

FIGURE 5. Left ventricular cardiac muscle after 60 minutes of coronary occlusion **(A)**, followed by 60 minutes of reperfusion **(B)**. (×16,500, reduced by 50 percent.)

myocardium may be, our results clearly indicate that revascularization of myocardium after 60 to 90 minutes of ischemic insult may not be attended with immediately demonstrable improvement in myocardial function. Periods of reperfusion longer than 60 minutes may be necessary for restoration of myocardial contractility.[15–17]

Infarct size after reperfusion: In experiments utilizing a closed chest experimental preparation,[7] Maroko et al.[15] have reported that infarct size as determined by S-T segment elevation and myocardial creatine phosphokinase activity can be markedly reduced by reperfusion after 3 hours of coronary occlusion. Similar results on myocardial structure have been reported by Ginks et al.,[18] who found a substantial circumferential reduction in infarct size after 7 days of reperfusion. This is understandable if it is realized that the degree of ischemic damage dimin-

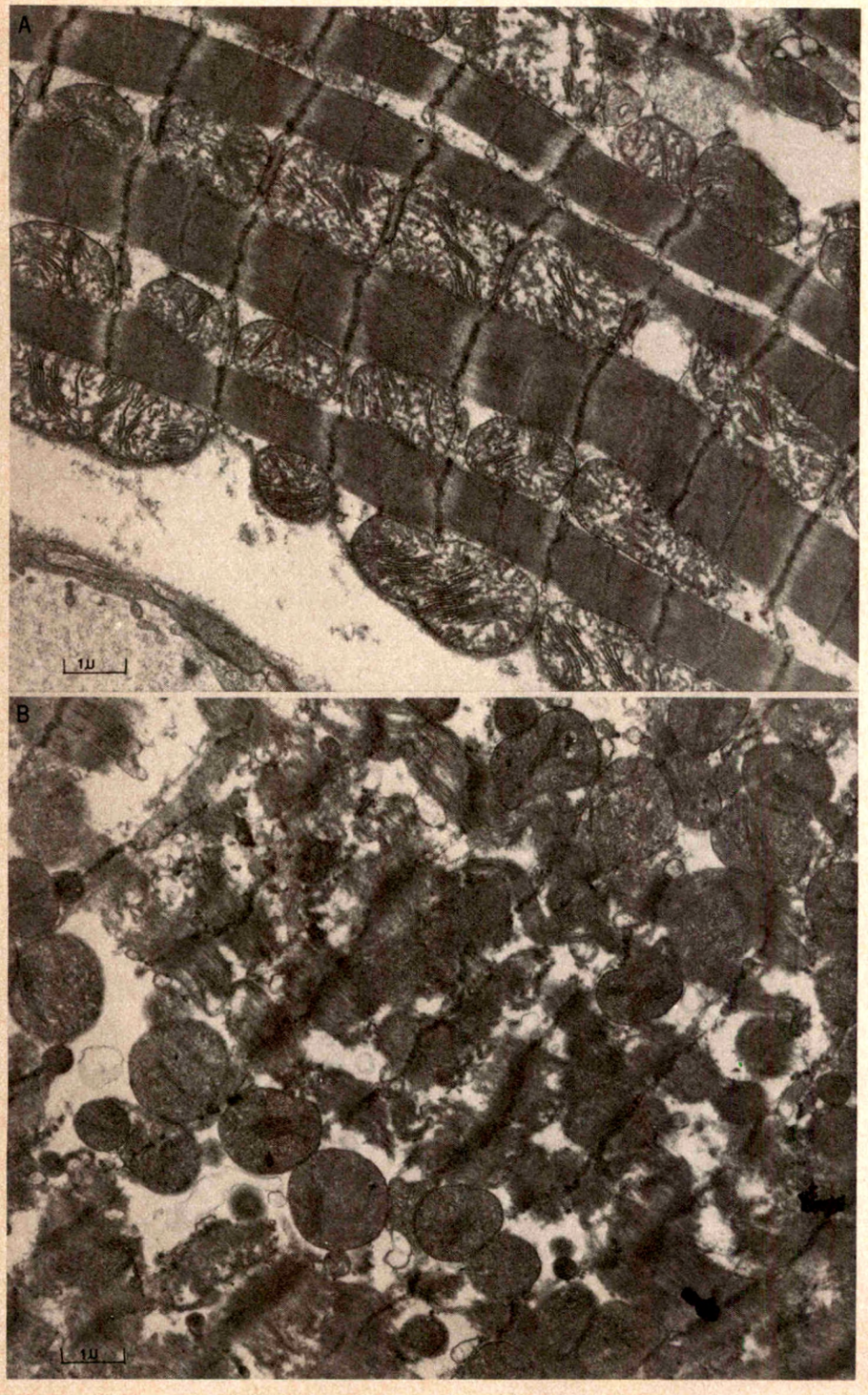

FIGURE 6. Left ventricular cardiac muscle after 90 minutes of coronary occlusion **(A)**, followed by 60 minutes of reperfusion **(B)**. (×16,500, reduced by 50 percent.)

ishes progressively from the central zone of maximal ischemia to the peripheral border zone of partial ischemia and that changes in this "twilight zone" between absolute ischemia and area of normal perfusion are reversible if reperfusion is prolonged beyond 60 minutes. This view is also substantiated by our data from myocardial surface electrograms recorded in the central zone of the infarct. Dissection of the left anterior descending coronary artery before its occlusion produced S-T segment elevation of 3.17 ± 1.25 mv (mean ± standard error of the mean). S-T segment elevation increased significantly ($P < 0.02$) within 15 minutes after coronary occlusion, and this trend was maintained throughout the period of ischemia. At the peak of the ischemic period the value was 11.33 ± 2.66 and it was still high (6.60 ± 1.49 mv) at the end of 60 minutes of reperfusion, a value not significantly low ($P > 0.1$) when compared with that at the end of the ischemic period. Slight but insignificant ($P > 0.05$) improvement in maximal left ventricular dP/dt noted in the group with 30 minutes of ischemia may partly be due to altered compliance of the ischemic zone, which changes from a relaxed noncontracting area to a contracted, edematous and stiff segment upon reperfusion. Our data on ultrastructure during reperfusion appear to support this hypothesis.

Myocardial high energy stores after reperfusion: Inability of myocardial contractility to recover after 60 minutes of reperfusion can also be examined in the light of our findings on high energy stores. Depressed high energy phosphate levels after 60 or 90 minutes of ischemia did not turn to normal upon reperfusion. Since the values for creatine phosphate, ATP and total nucleotides in this study are expressed in terms of wet tissue weight, it is possible that decreases in these variables after reperfusion of myocardium subjected to 60 and 90 minutes of ischemia may have been due to an increase in cell water.[23,26] This can not be entirely so because the ATP/ADP ratio was also depressed in reperfused myocardium after 60 or 90 minutes of ischemia. Since this ratio is a well known sensitive index of the status of oxidative phosphorylation, we suggest that the inability of the ischemic myocardium after 60 and 90 minutes of coronary occlusion to recover its high energy phosphate stores to control levels upon reperfusion may partly be due to a defect in the ability of mitochondria to generate energy.

Serum enzymes and myocardial ultrastructure after reperfusion: Serum enzyme determinations have been widely used in the diagnosis and assessment of myocardial infarction.[8,20–23] In this study an attempt was made to correlate directly the serum enzyme levels (CPK, GOT and LDH) in coronary sinus blood to the ultrastructure of the myocardium during experimentally induced ischemia and subsequent 60 minutes of reperfusion. Biopsy material and samples of coronary sinus blood were obtained simultaneously in the same hearts. The initial values indicated the effect of thoracotomy, pericardiotomy and dissection of the left anterior descending coronary artery on the enzyme activity in coronary sinus blood serum. Subsequent ischemia for 30, 60 and 90 minutes produced various degrees of change in enzyme levels, but the most dramatic changes were observed upon reperfusion, particularly in hearts subjected to 60 and 90 minutes of ischemia. All three enzymes studied (CPK, GOT and LDH) showed several-fold increases in activity levels ($P < 0.05$) in coronary sinus blood serum. This finding can be interpreted to reflect damage to the cell membranes and leakage of intracellular enzymes during reperfusion.

Actual breakdown of sarcolemmal membranes upon reperfusion of an ischemic myocardium has been demonstrated by several workers.[14,16,17,23–25] Functional impairment of cell membranes alone should be sufficient to provide such changes in enzyme levels, and this is particularly true of our group with 60 minutes of ischemia, which had the highest level of changes. There is no doubt that gross changes in ultrastructure are noticeable upon reperfusion in this group but these cells are by no means necrotic as they would be under the classic description of an infarct. It is also noteworthy that the highest degree of change in the surface electrocardiogram, noticed at the end of the ischemic period, did not correspond with the highest enzyme levels in coronary sinus blood serum, and in this respect our findings appear to differ from those of Maroko et al.[15] and Ginks et al.[18] Caution should therefore be exercised in estimating the degree of ischemia and the size of the ischemic area from the level of serum enzymes alone. The size of the ischemic area was essentially similar in all three groups (30, 60 and 90 minutes of ischemia) as were the serum enzyme levels at the end of the ischemic period. However, during the period of reperfusion there were dramatic differences that could be interpreted as indicating increased infarct size if a direct relation between enzyme levels and infarct size is accepted. It should be clear that functional damage to cell membranes is as important in this respect as the number of cells involved. The very steep rise of serum enzyme levels during reperfusion by comparison with the levels during ischemia would, in a clinical setting, suggest development of collateral blood flow.

Cell damage after reperfusion: Changes in myocardial ultrastructure due to acute ischemia and the effect of subsequent reperfusion have been amply reported,[14,16,17,23–26] and our findings are in essential agreement with previous studies. The two electron photomicrographs pertaining to each of the groups with 30, 60 or 90 minutes of ischemia belong to the same heart. Biopsy specimens for these studies were obtained from sites in the central area of the ischemic zone about 5 mm apart from each other. Comparison of Figures 4A, 5A and 6A clearly demonstrates the progression in damage to myocardial cells as the duration of ischemia is prolonged. All the recognized changes,[14,20,23,25,26] such as relaxed myofibrils, intracellular edema, swelling of the sarcoplasmic reticu-

lum and mitochondrial damage, decrease in electron density of the matrix and partial loss of cristae, can readily be seen ranging in degree from minimal (after 30 minutes of ischemia) to gross (90 minutes of ischemia). Reperfusion after a period of ischemia produces gross contraction of myofibrils and further damage to mitochondria and sarcoplasmic reticulum (Fig. 4B, 5B and 6B). Jennings et al.[14] have suggested that cell damage is reversible by reperfusion after 15 to 20 minutes of ischemia. About 50 percent of the myocardial cells in the ischemic zone are regarded as irreversibly damaged after 40 minutes of ischemia, and 60 minutes of absolute ischemia produces irreversible damage to about 100 percent of the cell mass in the ischemic area. Adverse effects of reperfusion such as breaking of sarcolemmal membranes have been shown by Kloner et al.[23] Furthermore, dramatic alteration in the electrolyte contents of the ischemic myocardium has been shown to occur upon reperfusion.[26]

It has been suggested[26] that damaged myocardial cell membrane will permit abnormal entry of calcium ion during reperfusion and will cause calcium overload.[14,17] Several authors[14,24,25] have described the appearance of dense bodies within the mitochondria at this stage, and these are regarded as calcium deposits. Our results and those of others[14,23–26] concerning contracted myofibrils in reperfused ischemic myocardium can be explained on the basis of elevated levels of intracellular calcium ion. It has also been suggested[28] that intracellular calcium overload is involved in myocardial fiber necrosis, and it is likely that this is the mechanism of the observed extensive ultrastructural damage brought about by reperfusion of the ischemic myocardium. Areas showing a high degree of partial contraction have been demonstrated during the early stages of ischemia in the peripheral zone of the ischemic myocardium.[24,25] Korb and Totovic[24] have suggested that these areas may be caused by an influx of blood plasma constituents from the surrounding nonischemic myocardium into this damaged area. If this is so, then their origin is very similar to that of the contracted myofibrils seen after reperfusion of ischemic myocardium.

Clinical implications: Our results suggest that changes brought about by 30 minutes of myocardial ischemia are reversible upon reperfusion and the same may be true for 60 minutes of ischemia. Ninety minutes of myocardial ischemia will produce serious biochemical and ultrastructural damage that may show further deterioration during the first 60 minutes of reperfusion. Longer periods of reperfusion may be beneficial, but further study is required to determine if areas of myocardial damage will improve after prolonged reperfusion. Complete salvage of grossly damaged areas that represent the very core of the myocardial infarct may not be possible unless reperfusion is established within 60 minutes, and in this respect we agree with the conclusions of Jennings et al.[14] However, this is not the heart of therapeutic and surgical strategy in the management of acute and progressing myocardial infarction. The major thrust of these measures is against the area of partial loss of perfusion that occupies the peripheral zone of the infarct. It has been shown[15–18] that substantial recovery, sometimes as much as 90 percent of the initial overall size of the infarct, can be made even after 3 hours of total coronary occlusion. This may therefore be regarded as a reasonable limit of time available for revascularization procedures. Further studies with prolonged perfusion of the ischemic myocardium are warranted in order to establish the pattern of recovery of the damaged heart cells, and these are currently in progress in our laboratory.

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Contractile and Biochemical Effects of Coronary Reperfusion After Extended Periods of Coronary Occlusion

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The effects of coronary reperfusion on recovery of regional myocardial contractility and high energy phosphate levels were studied in dogs after various periods of coronary occlusion. Segmental changes in myocardial contractility were measured by means of a strain gauge-tipped, two-pronged catheter probe that measures myocardial fiber shortening. The curves of contraction are sensitive to the effects of ischemia. Coronary occlusion resulted in a rapid replacement of fiber shortening by passive fiber lengthening. If coronary occlusion was released and blood flow restored within 45 minutes, myocardial contractility returned promptly; adenosine triphosphate and creatine phosphate values were restored to normal. With coronary occlusion of 1 hour or longer, contractility failed to return in the immediate postperfusion period, but delayed return was recorded after 2 weeks of reperfusion. The extent of such recovery varied with the duration of preceding occlusion. Thus, reperfusion after 1 hour of occlusion was followed by return of fiber shortening over the entire reperfused region. With 2 hours of occlusion, recovery occurred over 75 percent of the reperfused myocardium. With 3 hours of occlusion followed by reperfusion, recovery of contractility was only partial, comprising approximately 60 percent of the reperfused region. High energy phosphate content of the reperfused myocardium showed a similar pattern of recovery. With occlusion of longer duration, reperfusion failed to restore contractility to any significant extent. These findings indicate that reperfusion after coronary occlusion of 1 to 3 hours may restore contractility over a period of 2 weeks, but the extent of such recovery diminishes with the increase in the duration of occlusion.

With the advent of surgical revascularization of ischemic myocardium in man, it has become of clinical importance to establish the maximal period of coronary occlusion that is compatible with contractile recovery upon reperfusion. The factors that determine myocardial viability are numerous and remain ill defined.[1–5] A difference is known to exist between viability of the whole heart subjected to surgical anoxic arrest and that of regionally ischemic myocardium when only a segment of coronary circulation is interrupted. In coronary occlusion, the need for maintenance of contractile activity with its attendant demands for efficient aerobic metabolism plays a major role in increasing the severity of ischemic injury and in reducing survival time.[1,2]

Studies of the reversibility of myocardial ischemic injury by other investigators[6–11] have focused primarily on the immediate postperfusion period. Hamer,[12] on the other hand, suggested that slow contractile recovery may occur with reperfusion even after prolonged periods of coronary occlusion. In this study, whose preliminary results were first reported in 1971;[13,14] both the immediate and the delayed effects of coronary reperfusion were examined. Contractile recovery was

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studied by means of a strain gauge-tipped catheter probe that measures myocardial fiber shortening [15,16] by mapping segmental changes in myocardial contraction over the surface of the left ventricle.[16] The curves of cardiac contraction so obtained are extremely sensitive to the effects of ischemia and reperfusion.[16,17] Two types of contractile responses to reperfusion were recorded. If reperfusion occurred within 45 minutes of coronary occlusion, there was an immediate return of contractility. With extended periods of coronary occlusion, reperfusion failed to restore contractility in the early postperfusion period, but a delayed recovery of contractility occurred over a period of 2 weeks subsequent to reperfusion. Since high energy phosphates provide the energy for contractile functions of the myocardium,[18–20] a study of changes in adenosine triphosphate (ATP) and creatine phosphate (CP) content of the myocardium was undertaken. Changes in contractility were compared with alterations in high energy phosphate content of the reperfused myocardium.

Methods

Experiments were performed in 60 mongrel dogs weighing 15 to 22 kg and anesthetized with sodium pentobarbital (25 mg/kg) given intravenously. The trachea was intubated and artificial ventilation, using room air, was instituted by means of a Harvard respirator pump. Thoracotomy was performed in the fifth left intercostal space and the pericardium was opened anterior to the left phrenic nerve. The left anterior descending coronary artery was mobilized by dissection and a rubber-sheathed curved arterial clamp described previously[16] was used to produce intermittent occlusion of one of its major branches. Left ventricular pressure was monitored through a stiff-walled catheter directly connected to a Statham P23Db transducer system and an Electronics for Medicine recorder. Zero level for pressure measurements was set at the mid-chest position. Left ventricular end-diastolic pressure was recorded using higher sensitivity at the end-expiratory phase of the respiratory cycle.

Regional contractility: A strain gauge catheter probe that measures myocardial fiber shortening, previously described in detail,[15,16] was used to measure segmental changes in contractility. Briefly, the device consists of two strain gauge-bearing prongs mounted on a stylette. There is a linear relation between the spacing of the prongs and the strain in the gauges. The distance between the prongs is 2.5 mm, thus permitting study of the curves of contraction over small segments of myocardium. The prongs were extended to the outside of the catheter and were directly inserted into the subepicardial surface of the left ventricular wall. Only terminal points of the prongs were engaged into the myocardium. As described previously, to obtain smooth curves of fiber shortening devoid of deformities the prongs are positioned parallel to the axis of myocardial fibers.[15,16] As the prongs follow the course of fiber shortening in systole, curves of contraction are inscribed in an upward direction on a beat to beat basis. Deeper insertion or slippage of the prongs results in development of deformed curves. Maintenance of subepicardial placement of the prongs is essential for continuous recording of the curves of fiber shortening. The validity and stability of the measurements of these curves obtained with the strain gauge probe have been tested and reported in a series of publications.[15,16] In this study the probe was used primarily to demonstrate the directional changes in the curves of shortening after coronary occlusion and subsequent reperfusion. Curves of shortening as measured with the strain gauge probe are extremely sensitive to the effects of transient ischemia and reperfusion.[17]

Coronary occlusion: By occluding one of the major branches of the left anterior descending coronary artery, medium-sized areas of ischemia were produced.[17] By means of the strain gauge probe, control curves of contraction were obtained from the region supplied by the artery to be occluded. The probe was positioned in the center of this area and recordings were made continuously as the artery was occluded. In this manner, the exact time course of changes in the curves of contraction were studied. As the probe was inched away from the center toward the periphery, the ischemic zone was mapped out as the region in which contractility was lost and replaced by the inverted curve (inscribed downward) of passive fiber lengthening.[17]

In six control dogs, coronary ligation was made permanent. The ischemic area was studied for 3 hours after coronary occlusion. Thereafter, the chest was closed and the animals were restudied 2 weeks later following a protocol similar to that for the animals undergoing reperfusion except for omission of the release of coronary occlusion.

Coronary reperfusion: In 25 experiments in 15 dogs (Group I), the immediate effects of coronary reperfusion on recovery of contractility were studied after a period of coronary occlusion that ranged from 10 to 55 minutes. The occlusion clamp was released and blood flow restored at 10 minute intervals up to 30 minutes of occlusion and thereafter at 5 minute intervals. In 34 animals (Group II) the period of occlusion ranged from 1 to 5 hours. Possible return of contractility was studied for 2 to 3 hours after release of occlusion in each of the animals. If contractility failed to return, then the chest was closed in layers, pneumothorax was evacuated and the animals were allowed to recover. Possible delayed recovery of contractility was studied by reexamining the reperfused region 2 weeks later. Thoracotomy was performed and hemodynamics were measured in a manner similar to that of the initial study.

To study recovery of contractility, mapping of the reperfused region was carried out by means of the strain gauge probe. Since the distance between prongs of the probe is 2.5 mm, it is possible to differentiate segmental areas showing myocardial contraction (upwardly inscribed curve) from the adjoining noncontracting segments (inverted curve). As the probe was inched away from the center toward the periphery, the segmental changes in the curves were recorded. Schematic diagrams showing distribution of changes in curves were made using arteries and veins as the landmarks. A rough estimate of the area that registered curves of contraction was made and expressed as a percentage of the total reperfused region.

Biochemical measurements: Myocardial biopsy samples were taken by means of a bone rongeur precooled in liquid nitrogen as reported previously.[21] Biopsy samples were obtained from the center of the reperfused area and from the noninfarcted areas of the left ventricle. The myocardial samples were immediately placed (within 1 second) in precooled Freon 21®. The latter produces rapid and thorough freezing of the samples. The specimens were then transferred to and stored in liquid nitrogen. After the tissue was weighed, the frozen samples were pulverized and homogenized with 1 ml of perchloric acid per 100 mg tissue. Adenosine triphosphate (ATP) content was determined according to Adam[22] as described previously.[23] Creatine

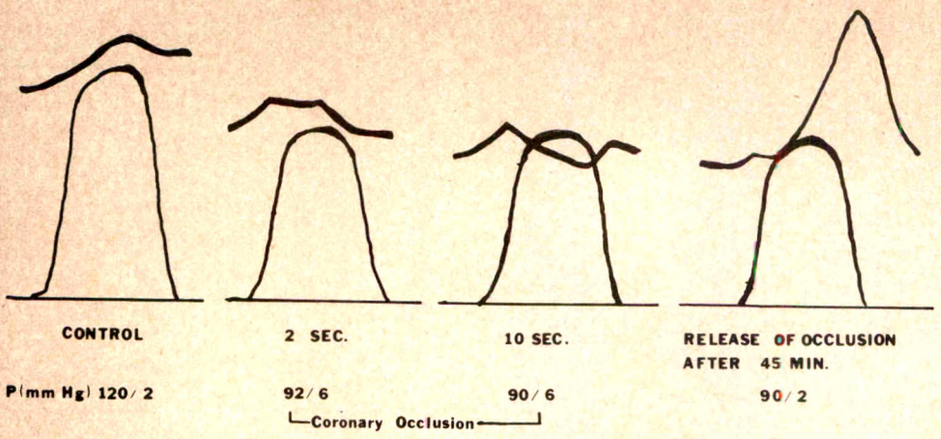

FIGURE 1. Effect of coronary reperfusion on the curves of myocardial contraction. In the control state the curve of myocardial contraction is inscribed in an upward direction. Two seconds after occlusion, the late systolic portion of the curve begins to show inversion. At 10 seconds the curve is inverted, indicating loss of fiber shortening and its replacement by passive fiber lengthening. After release of coronary occlusion at 45 minutes, the original upward inscription of the curve associated with an initial overshoot is restored, indicating recovery of contractility. P = left ventricular pressure.

phosphate (CP) was measured by utilizing the following reaction[23]:

$$CP + ADP \xrightarrow{CPK} C + ATP$$

where ADP = adenosine diphosphate and C = carbon. The adenosine triphosphate formed was subsequently determined as mentioned. The recovery of creatine phosphate was 95 percent ± 4 percent (standard error of the mean). Biopsy samples were taken at the time of the study of recovery of contractility. The results were expressed in micromoles per gram of tissue. In animals with 45 minutes of coronary occlusion, samples were taken 5 minutes after reperfusion. In animals with 1 to 3 hours of occlusion, samples were taken during the study for delayed recovery of contractility 2 weeks after reperfusion. Biopsy samples were also obtained from 5 sham-operated animals in which the same protocol was followed except for the omission of coronary ligation.

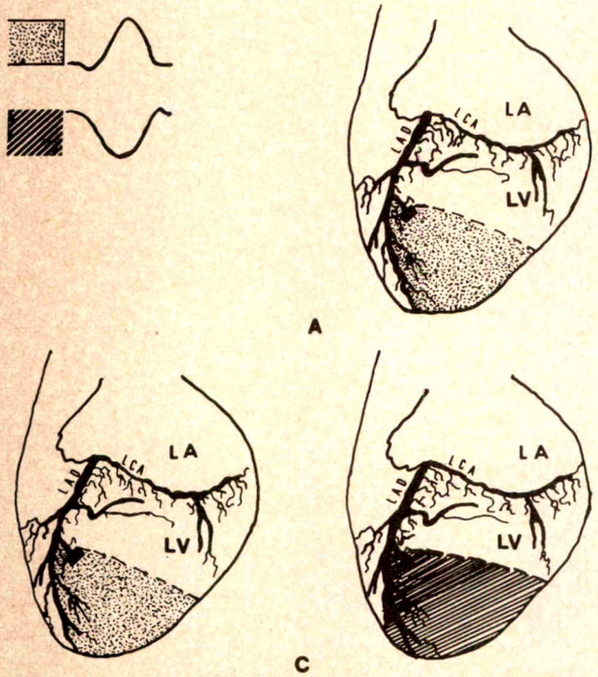

FIGURE 2. Recovery of contractility in the immediate postperfusion period. Schematic representation of the mapping of the reperfused region by means of the strain gauge catheter probe shows that reperfusion after 30 minutes **(A)** and 45 minutes **(B)** of coronary occlusion results in prompt return of contractility over the entire region (upward curve). However, reperfusion after 50 minutes of occlusion **(C)** fails to restore contractility (inverted curve). LA = left atrium; LAD = left anterior descending coronary artery; LV = left ventricle.

Histology: Random myocardial specimens were obtained for histologic examination from the center and periphery of the reperfused region as well as from the nonischemic area. The specimens were fixed in a solution of 10 percent formalin and stained with hematoxylin-eosin and Giemsa stains. The sections were examined independently of the knowledge of the experimental protocol. The presence of infarction was identified and its extent estimated from the relative amounts of normal and infarcted tissues in a given section, but histologic examination was not used to quantitate the total extent and distribution of infarcted myocardium in the reperfused region.

Results

Early Postperfusion Period

The systolic curve of myocardial contraction (fiber shortening) is inscribed upward. In diastole, corresponding to myocardial relaxation and fiber lengthening, the curve is inscribed downward (Fig. 1). Coronary occlusion resulted in an immediate decline in the amplitude of the curve of contraction. At 2 to 5 seconds, the late systolic portion of the curve was inverted and at 10 to 30 seconds the entire curve was inscribed downward, indicating loss of systolic fiber shortening and its replacement by dyskinetic passive fiber lengthening (Fig. 1). Release of coronary occlusion and restoration of blood flow resulted in a prompt return of the original upward inscription of the curve, indicating recovery of contractility. There was an initial overshoot in the amplitude of the curve of contraction coinciding with the phase of hyperemia (Fig. 1). This sequence of events in which the curve of contraction becomes inverted with coronary occlusion and returns to the upright inscription with release of occlusion could be repeated several times in the same animal. Reproducibility of these changes was established in 15 experiments, thereby demonstrating that the curve of contraction is extremely sensitive to the effects of ischemia and reperfusion.

Coronary occlusion was released at 10, 20 and 30

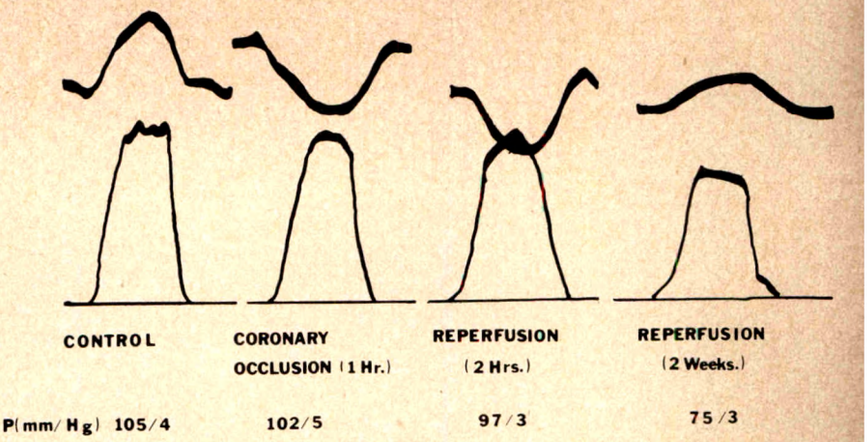

FIGURE 3. Effect of reperfusion after 1 hour of coronary occlusion. The inverted curve of passive fiber lengthening that followed coronary occlusion remained unchanged for several hours after release of occlusion. Two weeks later, however, the upward inscription of the curve was restored, indicating recovery of fiber shortening.

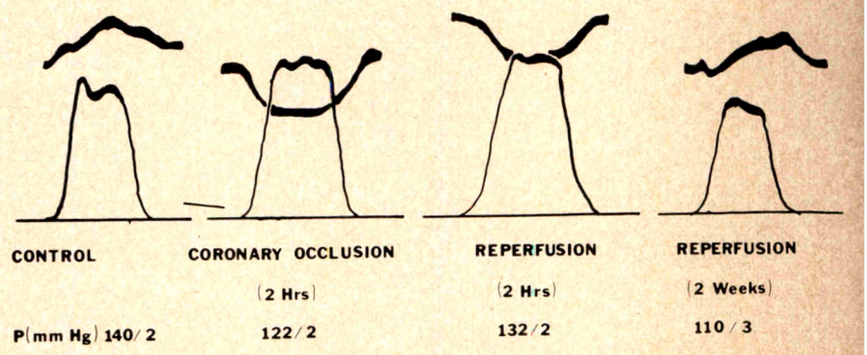

FIGURE 4. Effect of reperfusion after 2 hours of coronary occlusion. Release of occlusion failed to restore contractility in the immediate postperfusion period. Two weeks later, however, the upward curve of fiber shortening was registered, indicating return of contractility.

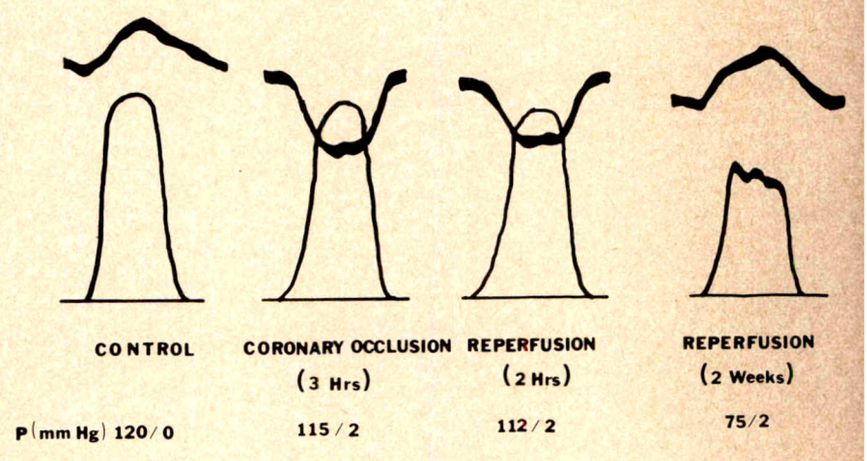

FIGURE 5. The inverted curve of fiber lengthening that followed coronary occlusion remained inverted for 2 to 3 hours after release of occlusion. After 2 weeks of reperfusion, however, the upward curve of myocardial contraction was again recorded.

minutes in three experiments each. The curve of contraction returned promptly in each instance. Subsequently, effects of reperfusion at 35, 40, 45, 50 and 55 minutes were studied in three experiments each. In all experiments with reperfusion occurring at 35, 40 and 45 minutes, recovery of contractility promptly followed the release of occlusion (Fig. 1 and 2). However, with reperfusion at 50 and 55 minutes, curves of contraction failed to return over a period of 2 hours during which the observations were made (Fig. 2).

Delayed Recovery of Contractility

As the duration of occlusion was increased from 1 to 5 hours, reperfusion failed to restore contractility over a period of 2 to 3 hours during which the observations were made (Fig. 3 to 5). When these animals were reexamined after 2 weeks of reperfusion, curves of contraction were recorded over the reperfused region; the extent of recovery of contractility varied with the duration of the preceding occlusion. In six dogs in which coronary occlusion was released after 1 hour, contractility returned over the entire reperfused region. A representative tracing (Fig. 3) and the schematic mapping of the reperfused region (Fig. 6) are shown. In eight animals with 2 hours of coronary occlusion followed by reperfusion, curves of fiber shortening were recorded over an average of 75 percent of the reperfused myocardium (Fig. 4 to 6). The

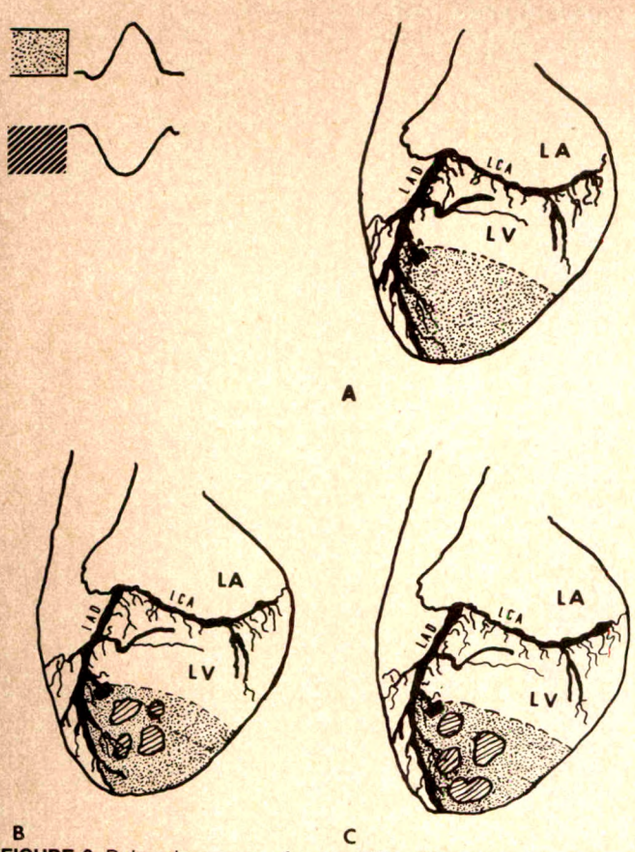

FIGURE 6. Delayed recovery of contractility at 2 weeks after reperfusion. Schematic representation of the mapping of the reperfused region is shown. **A,** in an experiment with 1 hour of coronary occlusion, curves of fiber shortening (upward curve) were recorded over the entire reperfused region. **B,** in an experiment with 2 hours of occlusion, the distribution of the curves of fiber shortening versus the curves of fiber lengthening (downward curve) indicated that contractility returned over approximately 75 percent of the reperfused region. **C,** in an experiment with 3 hours of occlusion, curves of fiber shortening were recorded over an area constituting approximately 60 percent of the reperfused region.

noncontracting myocardial segments were mostly clustered in the center of the reperfused region. In six of the eight animals with 3 hours of occlusion, 2 weeks of reperfusion resulted in only partial recovery of contractility. As seen in Figure 6, curves of contraction were recorded over an average of 60 percent of the reperfused region. Noncontracting segments were chiefly concentrated in the center and extended outward. In two animals, contractility failed to return. Of six animals with 4 hours of occlusion, only two showed some recovery of contractility over an estimated area of 15 to 20 percent of the reperfused region; in the remaining four animals, reperfusion failed to restore contractility. Of six animals with 5 hours of coronary occlusion, curves of contraction failed to return over most of the reperfused region.

In the group of six control animals in which coronary occlusion was not released, the inverted curve of dyskinesia was recorded over the ischemic area for 1 to 3 hours after ligation. Two weeks later when these animals were restudied, the ischemic myocardium showed either dyskinesia (inverted curve) or akinesia (flat curve). In none of these animals were curves of fiber shortening indicative of the recovery of contractility recorded over the ischemic region.

Biochemistry

There was a decrease in the myocardial adenosine triphosphate and creatine phosphate content of the nonischemic region of the left ventricle as compared with control values obtained from the sham-operated animals without coronary occlusion (Table I). This was particularly marked in animals with 3 hours of occlusion in which adenosine triphosphate decreased by 23 percent and creatine phosphate by 30 percent as compared with the control values. In view of these changes in the nonischemic zone, the reperfused region was compared with the control values obtained from the sham-operated animals. Reperfusion after 45 minutes of coronary occlusion resulted in complete restoration of both the adenosine triphosphate and creatine phosphate values. In animals with 1 to 3 hours of coronary occlusion, study after 2 weeks of reperfusion showed that changes in high energy phosphates varied with the duration of preceding coronary occlusion. Thus in animals with 1 hour of occlusion, myocardial adenosine triphosphate content of the reperfused region was 87 percent and creatine phosphate content was 95 percent of the control values. In animals with 2 hours of occlusion, adenosine triphosphate values were 75 percent and creatine phosphate values 83 percent of control levels. Reperfusion after 3 hours of occlusion resulted in adenosine triphosphate content that was 56 percent and creatine phosphate content that was 60 percent of control values.

Histology

Histologic examinations of the nonischemic area and the periphery of the reperfused region revealed no significant abnormalities. The center of the reperfused region in four animals with 1 hour of coronary occlusion showed no evidence of an infarct. In the remaining two animals, the infarcted tissue constituted 5 to 10 percent of the myocardial tissue in the section. In animals with 2 hours of occlusion, there were scattered focal areas of infarction that constituted 15 to 25 percent of the tissue in the section. In animals with 3 hours of occlusion, scattered areas of focal infarction constituted 30 to 40 percent of the myocardium in the section. In animals with occlusion of 4 or 5 hours, extensive infarction was seen in the section. These observations based on single histologic section obtained from the center of the reperfused region do not provide quantitative delineation of the distribution of contracting versus noncontracting segments.

Discussion

Development of methods to salvage ischemic myocardium is central to the evolution of a successful treatment program for acute myocardial infarction. It has recently been emphasized that there is a close

TABLE I

Effect of Coronary Reperfusion on Myocardial Adenosine Triphosphate and Creatine Phosphate Content (mean ± standard error)

	Adenosine Triphosphate (μmoles/g)		Creatine Phosphate (μmoles/g)	
	Nonischemic Region	Reperfused Region	Nonischemic Region	Reperfused Region
Control* (no. = 5)	5.45 ± 0.31	. . .	7.54 ± 0.24	. . .
45 min. (no. = 4)	5.59 ± 0.40	5.33 ± 0.39	7.74 ± 0.36	7.20 ± 0.30
1 hr (no. = 4)	5.20 ± 0.26	4.73 ± 0.53	7.57 ± 0.53	7.18 ± 0.76
2 hr (no. = 5)	5.02 ± 0.49	4.07 ± 0.65	6.98 ± 0.64	6.26 ± 0.53
3 hr (no. = 6)	4.18 ± 0.23	3.06 ± 0.19	5.27 ± 0.42	4.50 ± 0.35

* Sham-operated animals.

correlation between the number of myocardial contractile units lost and the mortality in acute myocardial infarction.[24–26] A number of physiologic and pharmacologic interventions have been shown to modify myocardial infarct size.[17,27] In our previous study,[17] we demonstrated that of cardiac stimulant drugs, isoproterenol is most likely to extend infarct size. An increase in afterload with methoxamine also results in an extension of infarct. Maroko et al.[27] have reported that interventions with oxygen-sparing agents such as propranolol may decrease the extent of ischemic injury. Hyaluronidase and corticosteroids[28] have also been credited with a similar effect. This ability to alter infarct size is essentially dependent upon the presence of ischemic but viable myocardial cells.

The factors that determine myocardial viability have not been precisely defined. The magnitude of ischemic injury is dependent on the state of cells prior to injury, the level of endogenous glycogen stores, cellular pH and ionic milieu, substrate availability and the state of collateral circulation.[1–3,29] The point of irreversible injury is controlled by the combined effects of metabolic breakdown of energy production, autolysis, protein denaturation, efflux from within the cell of enzymes, coenzymes and electrolytes.[3,10,29,30] Recovery is possible as long as the nuclei and cell membranes are intact.[1]

Contractile changes in early reperfusion period: In this study, the effects of ischemia and reperfusion were studied by means of a strain gauge-tipped catheter probe that measures myocardial fiber shortening.[15,17] The probe registers curves of myocardial contraction over localized segments of the ventricular wall,[16,17,31] which makes it possible to map the ischemic region before and after coronary reperfusion. Curves of contractility are extremely sensitive to the effects of ischemia.[16,17] Contractility decreases immediately and failure of contraction is complete within 15 to 30 seconds after coronary occlusion. Inability to contract is associated with passive distension (fiber lengthening) as ischemic myocardium yields to intraventricular pressure. This is reflected in the inversion or downward inscription of the curve in systole (dyskinesia) (Fig. 1). If coronary occlusion is released at any time within 45 minutes, the original upward inscription of the curve of myocardial contraction is promptly restored, indicating return of contractility (Fig. 2). This sequence of events is reproducible in the same animal as well as in a group of animals. These findings indicate that 45 minutes is the time limit of coronary occlusion compatible with an immediate return of contractility upon reperfusion. Results of similar previous studies have been variable. Thus, Tennant and Wiggers[6] suggested that recovery of contractility over 23 minutes of occlusion was only partial or absent. Blumgart et al.[7] using light microscopy observed that with occlusion of 25 to 45 minutes, gross detectible lesions were present that were roughly proportional to the duration of occlusion. Studies of Yabuki et al.[8] indicated that with release of occlusion in less than 30 minutes changes were only minimal; with occlusion of 45 minutes, however, necrosis was present. Krug et al.[9] reported that revival time for contractility after coronary occlusion was 30 to 45 minutes. Morphologic studies by Jennings et al.[10] have shown that after 45 minutes of ischemia, more than 60 percent of affected cells remained viable.

Delayed recovery of contractility: The delayed recovery of contractility observed after 2 weeks of reperfusion is a significant observation. The extent of recovery varied with the duration of preceding occlusion. Thus, after 1 hour of occlusion, contractile recovery occurred over most of the reperfused region (Fig. 3 and 6). As the duration of occlusion was increased to 2 hours, only 75 percent of the reperfused myocardium recovered (Fig. 4 and 6). With 3 hours of coronary occlusion, the extent of contractile recovery was further reduced to about 60 percent of the reperfused region (Fig. 5 and 6). With longer periods of occlusion of 4 to 5 hours, there were only a few focal areas registering curves of contraction. These findings, originally observed in 1971,[13] constituted the

first demonstration of regional functional recovery and reversal of paradoxical motion of ischemic myocardium upon reperfusion after extended periods of coronary occlusion. Study of the high energy phosphate metabolism in the reperfused myocardium, the preliminary report of which was published earlier,[14,32] indicates that corresponding to the contractile recovery, there occurred resynthesis of myocardial high energy phosphates. Coronary occlusion results in depletion of myocardial adenosine triphosphate stores.[18–20] Reperfusion after 1 hour of coronary occlusion resulted in almost complete restoration of adenosine triphosphate and creatine phosphate values. With longer periods of occlusion there was a progressive decrease in the recovery of these values after reperfusion (Table I). Since adenosine triphosphate provides the energy for contractile functions of the myocardium,[18–20] the parallel seen between resynthesis of adenosine triphosphate and recovery of contractility is of significance.

In a recent study, Ginks et al.,[33] using epicardial electrograms and myocardial enzymes, showed that reperfusion after 3 hours of coronary occlusion resulted in a decrease in infarct size at 1 week. On the other hand, studies in the immediate postperfusion period after coronary occlusion of 3 to 5 hours by Lang et al.[34] and by Bresnahan et al.[35] have suggested hemodynamic and metabolic deterioration and hemorrhagic extension of infarct. It seems to us, however, that contractile recovery can occur even after prolonged periods of ischemia, but the process is a slow one extended over a period of weeks. These observations confirm the contention of Hamer,[12] who suggested that slow contractile recovery is possible with reperfusion even after prolonged periods of occlusion. One of the factors contributing to myocardial salvage may be the fact that not all myocardial fibers are unalterably necrosed at the same time. In a given population of myocardial fibers there seem to be various degrees of biologic resistance to ischemic injury. Thus, contracting and noncontracting fibers were found to lie adjacent to each other. Whether this difference is dependent merely on the presence or absence of collateral circulation or is related to an intrinsic variation in metabolic characteristics of fibers is not known. In our previous study on coronary occlusion,[17] we showed that interposed between the central zone of complete ischemia and the nonischemic myocardium is an intermediate zone of partial ischemia in which contractility is diminished but not lost. Lushnikov[36] and Cox et al.[37] described a similar zone by means of histochemical studies. Diminished contractility of the myocardium in the intermediate zone with attendant decrease in its energy requirements will have the effect of prolonging its viability in the face of diminished oxygen delivery.[38]

Clinical implications: It may be concluded that at least partial salvage of ischemic myocardium is possible by coronary reperfusion even after extended periods of coronary occlusion. However, such recovery may not occur in the immediate postperfusion period but may require a period of 1 to 2 weeks. Although one must be cautious in extrapolating results of canine experiments to patients, these findings have obvious clinical application to the surgical revascularization of ischemic myocardium in man.

Acknowledgment

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Maximal Revascularization (Reperfusion) in Intact Conscious Dogs After 2 to 5 Hours of Coronary Occlusion

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Acute infarction was produced in intact conscious dogs by inflating a previously implanted balloon cuff around the left anterior descending coronary artery. The artery was occluded in 26 control dogs and reperfused by deflating the balloon cuff after 2 hours of occlusion in 19 dogs (group II) and after 5 hours in 11 dogs (group III). Serial studies were performed and repeated after 48 hours and 7 days. All three groups revealed hemodynamic and metabolic deterioration with coronary occlusion and infarct production. Immediately after reperfusion, arrhythmias developed in groups II and III and persistent ventricular tachycardia was present 2 to 3 hours after reperfusion in 74 percent of animals in group II and 82 percent of those in group III compared with 6 percent and 13 percent incidence rates at corresponding times in control dogs. Q waves developed in 83 percent of animals in group II and 100 percent of those in group III but in only 12 and 27 percent of control animals at corresponding times. Hemodynamic deterioration was accelerated in the postreperfusion period in both groups II and III. Angiographic assessment revealed improvement in 42 percent of dogs in group II, but in none of those in group III after reperfusion. Myocardial oxygen extraction diminished to subnormal levels after reperfusion, indicating either reactive hyperemia or shunting effect. Mortality was not significantly influenced by reperfusion. Infarct size was more than 15 percent of ventricular mass in 92 percent of control dogs and in 100 percent of dogs in group III, but in only 50 percent of those in group II.

The data indicate that reperfusion in conscious dogs representing early, noninvasive maximal revascularization under ideal circumstances fails to prevent deterioration or death; instead it hastens the development of arrhythmias and myocardial injury. Reperfusion, although deleterious in the first few hours, can reduce infarct size if performed after 2 hours, but not after 5 hours, of occlusion.

Acute myocardial infarction continues to be a major cause of death in spite of strides in treatment made in the past decade. In many cases the mortality and subsequent complications depend on the total mass of myocardium involved in infarction.[1–4] Studies in experimental myocardial infarction have suggested that it is possible to alter the ultimate size of the infarcted tissue by interventions applied early in the course of evolution of infarction[5,6]; the jeopardized zones of myocardium may respond to favorable interventions, whereas blighted and necrotic zones are unlikely to respond.[7] Because the major determinant of ischemic injury is an imbalance between supply and demand of oxygen and other substrates, it is logical to expect beneficial results from an increase of blood flow to the affected area. This restoration of blood flow may allow the border zones to escape infarction and recover partly or completely. Suggestions that this may be the case in man have come from results of several studies employing

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streptokinase in the early stages of acute myocardial infarction,[8–11] a form of medical revascularization. A few centers have even employed surgical revascularization using aortocoronary bypass grafts in the early stages of infarction and have interpreted the results as satisfactory.[12–14]

This study was initiated to test the hypothesis that early revascularization of the ischemic myocardium in evolving infarction can alter the course favorably and possibly reduce infarct size. To achieve maximal revascularization, restoration of normal blood flow was attempted by reperfusing the occluded coronary artery. A model of intact conscious dogs was employed to preserve all the reflexes, study the influence of infarction alone rather than that of associated surgery and anesthesia and allow collection of data pertaining to the whole animal rather than to a portion of its myocardium. Since the initiation of this study, Maroko et al.[15] and Ginks et al.[16] have presented data in anesthetized dogs indicating that coronary arterial reperfusion can improve local myocardial function and reduce infarct size.

However, Lang et al.[17] have reported quite opposite effects. They found serious abnormalities in hemodynamic status, metabolic function and morphologic features of the heart when they reperfused seven dogs after 3 hours of coronary occlusion. Also, Banka et al.[18] found that reperfusion after 1 hour of occlusion resulted in further accentuation of contractile abnormalities in the ischemic zone of the myocardium in each animal and in the border zone in four of six animals. They further reported that after 2 and 3 hours of coronary occlusion, reperfusion was uniformly followed by further decreases in function of both the ischemic and border zones.

Studies in 56 intact conscious dogs involving electrocardiographic patterns, left ventricular function, myocardial metabolic derangements, infarct size and mortality are presented in this communication.

Methods and Materials

Procedures: Large mongrel dogs weighing 25 to 30 kg were operated on under general anesthesia, and through a thoracotomy a balloon cuff device (Brunswick Manufacturing Company, Quincy, Massachusetts) was implanted around the left anterior descending coronary artery. The dogs were then allowed to recover for 7 to 10 days. With use of local anesthesia and light morphine sedation (10 to 15 mg subcutaneously) with animals in the awake state, the femoral and carotid arteries and jugular vein were exposed. A transducer-tipped catheter (Millar Instruments, Houston, Texas) to obtain high fidelity recordings of pressure and derivatives of pressure was positioned in the left ventricle, a thermistor-tipped catheter was placed in the pulmonary artery and other catheters were positioned in the aorta, coronary sinus and right atrium under fluoroscopic control for constant pressure monitoring, sampling, thermodilution cardiac output determinations and angiography. The electrocardiogram was monitored throughout with lead V_4. Control measurements were then made of pressures from the chambers cited, first derivative of left ventricular pressure (dP/dt), heart rate, cardiac output, calculated stroke volume and work, oxygen and lactate content of arterial and coronary sinus blood, calculated oxygen and lactate transmyocardial extraction data and left ventricular angiogram with calculated ejection fraction.

TABLE I

Case Material

First series (survived for 2 hours)	35
Control (occlusion maintained)	16 (group IA)
Reperfusion after 2 hours	19 (group II)
Second series (survived for 5 hours)	21
Control (occlusion maintained)	10 (group IB)
Reperfusion after 5 hours	11 (group III)

After the recording of control measurements, myocardial infarction was produced in the intact conscious animal by slight modification of the technique of Hood et al.[19] The Silastic® tubing connected to the balloon cuff device around the left anterior descending coronary artery was exteriorized and the balloon progressively inflated in stepwise fashion over the next 10 to 15 minutes with use of an insulin syringe and manual control until signs of acute ischemia appeared. These signs included peaked T waves, tachycardia and increased left ventricular end-diastolic pressure (Fig. 1 to 3). The balloon was further inflated to ensure complete occlusion of the left anterior descending coronary artery. Arrhythmias appearing in the first 30 minutes after occlusion were treated with lidocaine (a bolus injection of 40 mg followed by infusion of 1 to 4 μg/min). All measurements were then serially repeated. In addition, coronary angiography was carried out before and after reperfusion to visualize an occluded left anterior descending coronary artery before reperfusion and a patent artery after reperfusion. Heparinized saline solution was infused to maintain patency of all the catheters throughout the procedure, the total amount of heparin used being 15 mg or approximately 1,500 units per hour.

Studies: In the first series (Table I), 35 animals survived for 2 hours, when they were randomly divided into two groups. The balloon cuff was kept inflated and the left anterior descending coronary artery remained occluded in 16 control dogs. In 19 dogs the balloon was deflated after 2 hours of occlusion to allow the artery to reopen, thereby achieving reperfusion and maximal revascularization of the area. The patency of the artery after reperfusion was angiographically confirmed in each animal. In addition, electrocardiographic and metabolic changes (presented under Results) permitted confirmation of patency of the artery after deflation of the balloon cuff.

In the second series, 21 dogs survived for 5 hours and were divided into two groups. Ten in which the artery remained occluded served as control animals and the other 11 underwent reperfusion. For purposes of analysis, the data for both control groups have been combined. Thus, of 56 dogs, 26 served as control animals (group I), 19 underwent reperfusion after 2 hours (group II) and 11 underwent reperfusion after 5 hours (group III).

The short-term studies were carried out for 5 hours after infarction (2 hours before and 3 hours after reperfusion) in the first series of dogs and for 7 hours (5 hours before and 2 hours after reperfusion) in the second series, and the dogs were then allowed to recover. Daily electrocardiograms including 1 minute rhythm strips were recorded. All surviving dogs underwent repeat cardiac catheterization studies, 7 days after infarction in the first series and 48 hours after infarction in the second series. The dogs were then killed, and the heart removed. The left ventricle was sectioned to obtain 1 cm thick slices and photographed, and the area of the infarcted myocardium as well as normal muscle was de-

termined. In addition, the infarcted myocardium was removed from each slice and the infarcted and noninfarcted portions were weighed.

Statistical methods: Student's t test was employed to detect significant differences between the control and study animals, and the chi square test was employed to compare the frequency of events in these groups.

Results

Heart rate: After increasing sharply during infarction, the heart rate stabilized and was similar in all groups until the time of reperfusion (Fig. 4). In group II, soon after reperfusion the rate increased and became more rapid 2 hours later because of the development of persistent ventricular tachycardia. Dogs in group III, who underwent reperfusion after 5 hours of infarction, also exhibited a sharp increase in heart rate after reperfusion. At the time of the second study the heart rate in both study groups was similar to that of the control group.

Ventricular arrhythmia: Premature ventricular

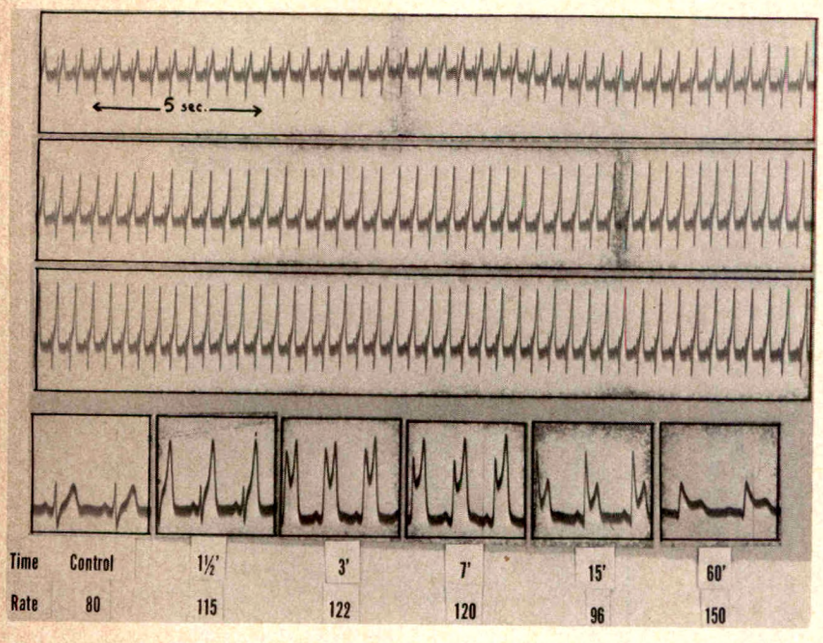

FIGURE 1. Changes in electrocardiogram with acute infarction. The **top three panels** are continuous strips of lead V_4 (paper speed 10 mm/sec) showing progressive peaking of the T wave after occlusion of the left anterior descending coronary artery. Within 1 minute the height of the T wave has doubled. The **bottom panel** shows the change in the heart rate (beats/min) and configuration of S-T segment and T waves at 1 1/2, 3, 7 and 15 minutes (paper speed 25 mm/sec) and 1 hour (paper speed 50 mm/sec) after infarct production.

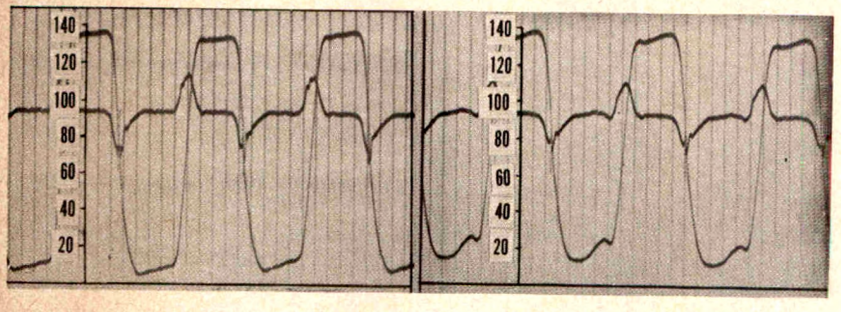

FIGURE 2. Changes in left ventricular pressure **(lower tracing)** and dP/dt **(upper tracing)** with acute infarction. The left ventricular pressure before infarction **(panel A)** is normal. The end-diastolic pressure 15 minutes after infarction **(panel B)** is 23 mm Hg, an increase of 13 mm Hg from the preinfarction value of 10 mm Hg.

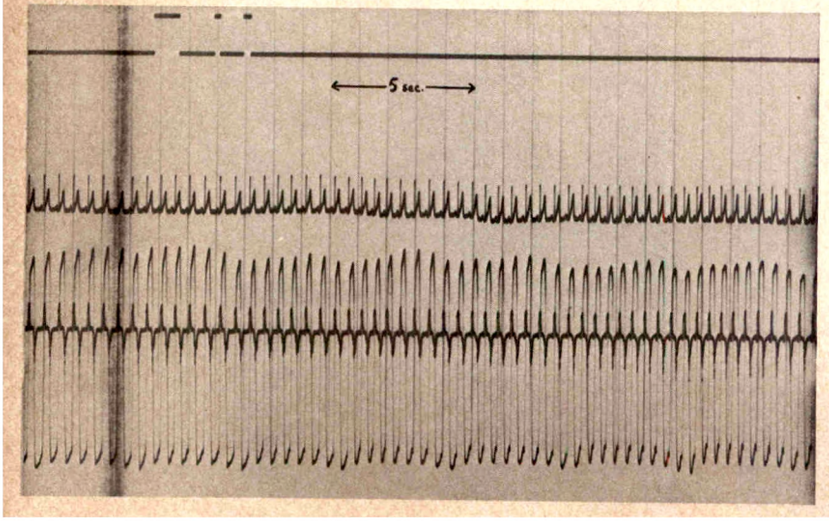

FIGURE 3. Changes in electrocardiogram and left ventricular pressure with acute infarction. Continuous strip (paper speed 10 mm/sec) showing electrocardiographic lead V_4 at top, high fidelity left ventricular pressure recorded by manometer-tipped catheter below it and its first derivative (dP/dt) in the middle of left ventricular pressure. At the time of the first mark, the left anterior descending coronary artery is occluded, resulting in immediate peaking of T wave and an increase in heart rate and left ventricular end-diastolic pressure.

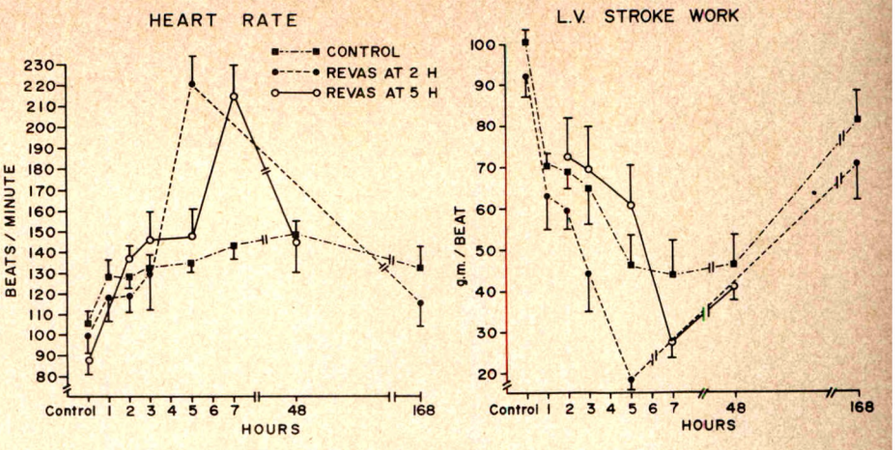

FIGURE 4. Changes in heart rate and left ventricular stroke work. The **left panel** depicts mean values of heart rate with standard error of the mean. The heart rate in group II, undergoing reperfusion at 2 hours (H), was significantly higher than control at the 5th hour (3 hours after reperfusion) with P value <0.01. The heart rate of group III, reperfused at the 5th hour, was significantly higher than control ($P<0.05$) at the 7th hour. The **right panel** shows a significant reduction of stroke work after reperfusion in both groups II and III ($P<0.05$). L.V. = left ventricular; REVAS = revascularization.

contractions and short runs of ventricular tachycardia were frequent in the first 30 minutes after infarction and were treated with lidocaine. At 2 hours after infarction, the rhythm was generally stable. In group II, within 20 to 120 seconds of reperfusion, frequent, repetitive and multiformed premature ventricular contractions developed in *each* animal and progressed to prolonged periods of ventricular tachycardia alternating with sinus tachycardia. The duration of episodes of ventricular tachycardia kept increasing until persistent ventricular tachycardia with multiformed irregular beats became the rule. The difference between the frequency of this arrhythmia in groups I and II at the 3rd and 5th hours after infarction was highly significant ($P<0.01$). After the initial experience of refractoriness of these arrhythmias to lidocaine, no attempt was made to treat them.

The pattern of arrhythmia in animals in group III undergoing reperfusion after 5 hours of infarction was similar to those undergoing reperfusion after 2 hours of infarction, and persistent ventricular tachycardia at the 7th hour of infarction was significantly more frequent than in the control group ($P<0.05$) (Table II). Among control animals not only did fewer dogs have ventricular tachycardia so early but also the arrhythmia was rarely persistent. However, at 24 hours the pattern in all groups was similar and ventricular tachycardia was almost universal. During recovery in the next 7 days, no significant difference was observed between the control animals and those undergoing reperfusion.

Q waves: Lead V_4 was monitored throughout the acute study. Significant and pathologic Q waves of 25 msec or longer duration were not present in any animal before infarct production. In the control group they generally developed after 5 hours (Table III). In group II pathologic Q waves were not present in any dog at 2 hours just before reperfusion but developed rapidly in 68 percent of the animals within 10 minutes of reperfusion. Either a very small insignificant Q wave widened or an initial R wave lost its amplitude and was quickly replaced by a Q wave (Fig. 5). The rapidity with which these changes developed can be seen in Figure 6. Ultimately, however, there was no difference between the control and reperfusion groups since the development of Q waves was almost universal. Dogs in group III also had a high incidence

TABLE II

Incidence Rate (%) of Episodic and Persistent Ventricular Tachycardia at Various Intervals After Infarct Production

Post-infarction Intervals (hr)	Episodic VT			Persistent VT		
	I	II	III	I	II	III
1	8	0	27	0	0	0
2	19	10	18	0	0	0
3	23	69	27	0	58†	9
5	46	79	73	6	74†	18
7	100	...	100	13	...	82*
24	100	100	100	100	83	100
48	93	81	71	31	20	0
72	14	8	...	0	0	...
168	0	0	...	0	0	...

*Significant difference from group I ($P<0.05$).
†Significant difference from group I ($P<0.01$).
I = control group; II = group undergoing reperfusion 2 hours after infarct production; III = group undergoing reperfusion 5 hours after infarct production; VT = ventricular tachycardia.

TABLE III

Incidence Rate (%) of Significant Q Waves at Various Intervals After Infarct Production in Survivors

Interval (hrs)	Group I	Group II	Group III
2	4	0	9
3	12	68	18
5	27	83	45
7	50	...	100
24	89	80	100

Group I = control group; Group II = group undergoing reperfusion 2 hours after infarct production; Group III = group undergoing reperfusion 5 hours after infarct production.

rate of rapidly developing Q waves immediately after reperfusion.

Cardiac output, stroke volume and stroke work: Throughout the acute study, cardiac output, stroke volume and stroke work progressively deteriorated after infarction in the control group (Table IV, Fig. 4) and were returning toward normal at the time of follow-up study. In both groups II and III, reperfusion resulted in a steeper short-term decline in these values, mostly because of concomitant ventricular tachycardia. The differences between values in these groups and the control group were not statistically significant, except in the immediate postreperfusion state when these hemodynamic data were worse in groups II and III than in control dogs.

Left ventricular pressures and dP/dt: In both reperfusion groups, the abnormalities in end-diastolic and developed pressure and dP/dt were accentuated in the immediate postreperfusion period concomitant with ventricular tachycardia (Fig. 7). At the time of repeat catheterization, there were no significant differences between the control and reperfusion groups. The end-diastolic pressure was significantly increased in all groups at the time of repeat study ($P < 0.01$).

Left ventricular contractility index: The velocity of contractile element (Vce) was calculated according to the method of Mason et al.[20] by relating the dP/dt and developed pressure during isovolumic systole recorded by manometer-tipped catheters. The value of Vce at a developed isovolumic pressure of 40 mm Hg is presented in Table V. Serial changes in this value reflect alterations in the contractile state,[21] which was depressed in all three groups after infarction. Reperfusion in groups II and III did not result in any significant difference from the control group.

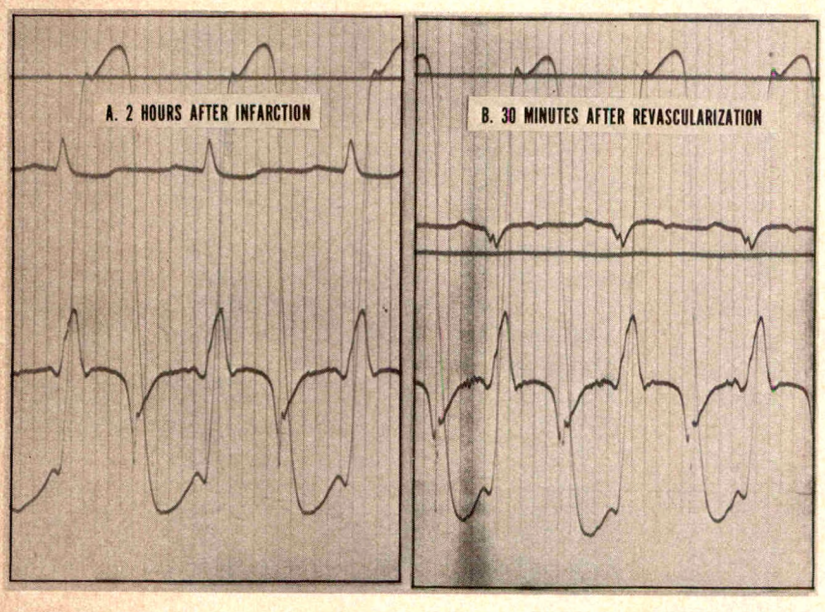

FIGURE 5. Effect of reperfusion on electrocardiogram and left ventricular pressure. The electrocardiogram (lead V_4), left ventricular pressure and its first derivative (dP/dt) are recorded at a paper speed of 100 mm/sec with time lines 0.04 second apart. Lead V_4 reveals a prominent R wave in **panel A,** 2 hours after infarction and immediately preceding reperfusion. **Panel B,** recorded 30 minutes after reperfusion (revascularization), reveals a dramatic change in QRS configuration; the same lead V_4 now has a QS pattern.

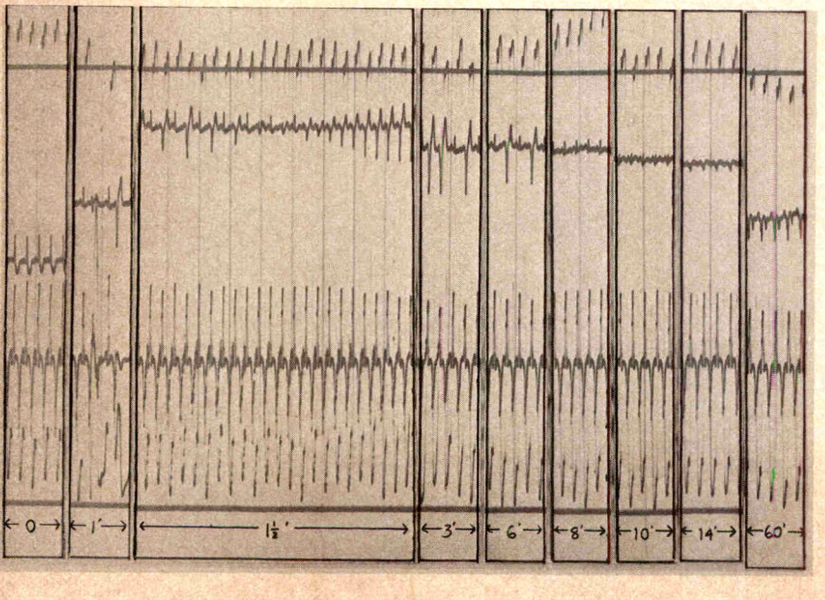

FIGURE 6. Immediate effects of reperfusion on electrocardiogram. Records of electrocardiogram (lead V_4), together with left ventricular pressure and its dP/dt at slow paper speed (10 mm/sec with time lines 1 second apart) reveal the rapidity of changes after revascularization (reperfusion). The numbers at the bottom indicate the time in minutes after reperfusion. At zero time a prominent R wave is recorded in lead V_4; after 1 minute the height of the R wave is reduced and premature ventricular contractions appear. At 1 1/2 minutes, premature contractions increase, leading to ventricular tachycardia. Progressive reduction in the amplitude of the R waves is noted in the sinus beats and at 10 minutes they are very small. At 14 minutes, QS configuration is seen and at 60 minutes QS configuration with inverted T waves is recorded.

TABLE IV

Cardiac Output and Stroke Volume

	Group I		Group II		Group III	
Interval (hr)	CO	SV	CO	SV	CO	SV
Preinfarction	6.11 ± 0.67	59.7 ± 7.2	5.44 ± 0.46	56.4 ± 5.3	. . .	. . .
1	5.38 ± 0.48	46.5 ± 5.5	4.64 ± 0.81	41.5 ± 6.2	. . .	. . .
2	5.12 ± 0.72	42.8 ± 6.0	4.37 ± 0.58	38.3 ± 3.6	5.51 ± 0.58	40.3 ± 4.0
3	4.93 ± 0.81	40.5 ± 6.4	3.88 ± 0.64	30.8 ± 4.2	5.15 ± 0.46	38.8 ± 5.4
5	3.95 ± 0.39	28.8 ± 2.3	2.91 ± 0.44	15.3 ± 3.7	5.16 ± 0.51	35.6 ± 3.2
7	4.30 ± 0.54	28.5 ± 2.7	. . .	. . .	3.75 ± 0.48	17.9 ± 2.2
48	4.20 ± 1.10	32.8 ± 6.9	. . .	. . .	4.89 ± 0.69	37.2 ± 9.2
168	6.13 ± 0.74	46.4 ± 5.9	4.51 ± 0.67	42.2 ± 6.2	. . .	. . .

CO = cardiac output in liters/min; SV = stroke volume in ml/beat.

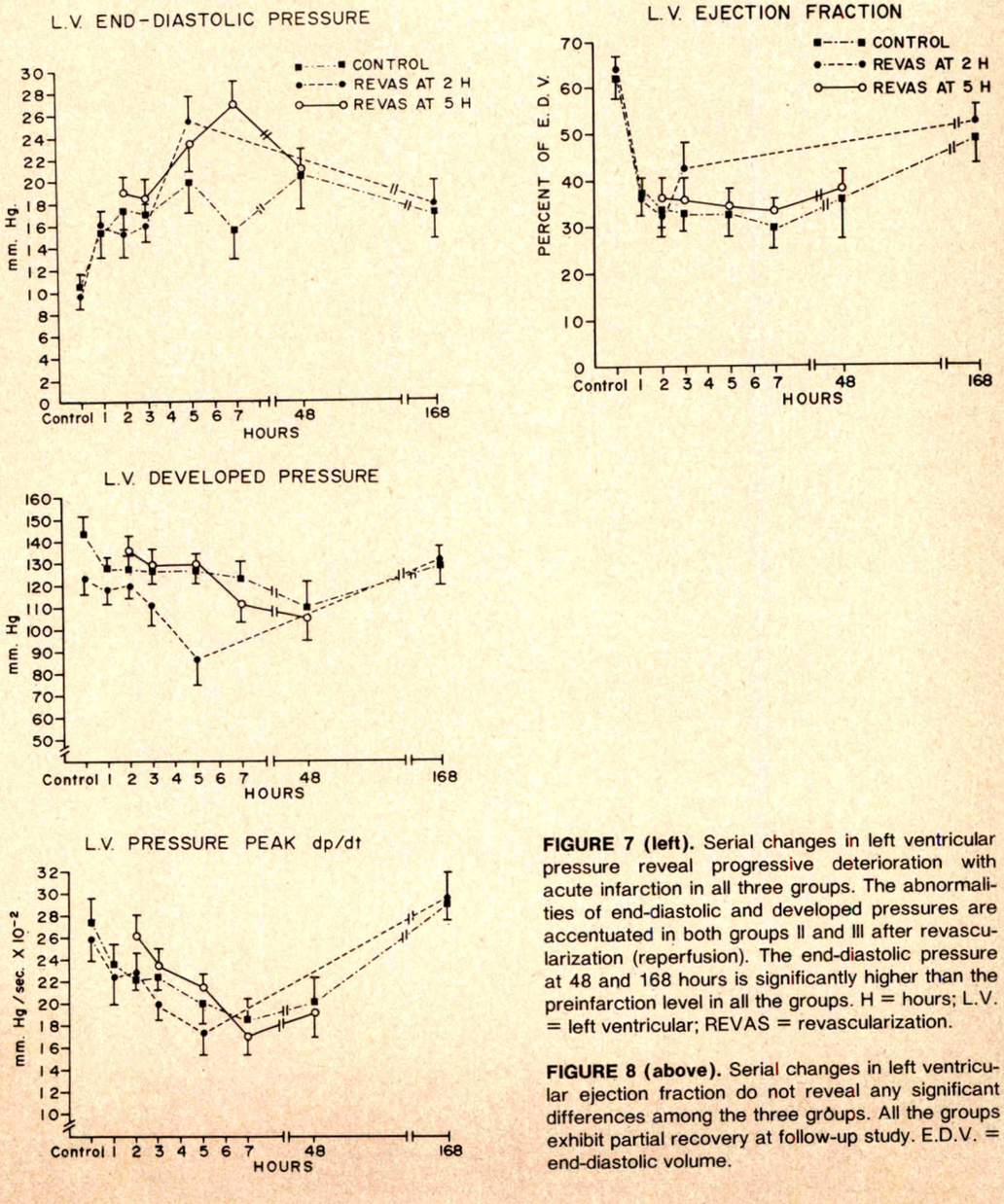

FIGURE 7 (left). Serial changes in left ventricular pressure reveal progressive deterioration with acute infarction in all three groups. The abnormalities of end-diastolic and developed pressures are accentuated in both groups II and III after revascularization (reperfusion). The end-diastolic pressure at 48 and 168 hours is significantly higher than the preinfarction level in all the groups. H = hours; L.V. = left ventricular; REVAS = revascularization.

FIGURE 8 (above). Serial changes in left ventricular ejection fraction do not reveal any significant differences among the three groups. All the groups exhibit partial recovery at follow-up study. E.D.V. = end-diastolic volume.

Ejection fraction and regional function: Selective left ventriculograms demonstrated definite areas of akinesia and dyskinesia in every animal in each group after infarction with reduction of ejection fraction. No significant differences in serial ejection fractions were observed among the three groups (Fig. 8) and in all animals repeat catheterization studies demonstrated improvement in values over those of the acute stage. The magnitude and extent of the dyskinetic or akinetic segment did not change in the control group between 2 and 5 hours after infarction. In group II, improvement was seen in 42 percent of dogs 1 hour after reperfusion (Fig. 9). No such improvement was found in group III after reperfusion at 5 hours.

Myocardial metabolic derangements: The transmyocardial oxygen extraction was calculated from arteriovenous oxygen difference as a fraction of arterial content [(arterial-venous/arterial)]. With the production of infarction, the extraction value increased in all groups (Fig. 10). In groups II and III, it diminished acutely (immediately after reperfusion) and during the next 2 to 3 hours was less than the preinfarction level. This sharp and sudden change was a valuable indicator of acute alteration in myocardial blood flow with reperfusion. At the time of follow-up catheterization, the values were returning toward normal in all three groups. The difference between groups I and III was significant at 48 hours ($P < 0.05$), but on the 7th day no difference was observed between the control and reperfusion groups. The responses of transmyocardial lactate extraction in different animals varied; the mean values for the three groups were not significantly different from each other.

Mortality: The overall mortality rates in the three groups were similar (31, 21 and 36 percent, respectively). All the deaths occurred within 24 hours, except for one death after 48 hours in group II. Three animals died during monitoring and experienced ventricular fibrillation at a time when their left ventricular systolic and diastolic pressures were comparable with values in the rest of the group; none had pulmonary edema or severe hypotension. In addition, primary ventricular fibrillation developed during monitoring in four other dogs, but these animals were successfully resuscitated.

Infarct size: In the control group, the infarct size averaged 30 percent of the left ventricular mass. In 2 of 26 dogs the infarct was less than 15 percent of the left ventricular mass and was considered small. In 9 of 18 dogs of group II, the size of the infarct was less than 15 percent of the left ventricular mass. The difference in the frequency of small infarcts, 50 percent in group II versus 8 percent in the control group, was significant ($P < 0.05$). However, in the other nine dogs of group II infarct size ranged from 20 percent to 44 percent of left ventricular mass and in six was more than 30 percent. Therefore, although the infarct was smaller than expected in half the group, its size was uninfluenced in others, and in some dogs was actually larger and hemorrhagic (Fig. 11). The average infarct size for all animals in group II was 20 percent of left ventricular mass; the difference from values in the control group was not statistically significant. Infarct size in animals in group III averaged 34 percent. None of the 11 animals had small infarcts (less than 15 percent of left ventricular mass). Thus, this group did not differ from the control group either in average infarct size or in frequency of smaller infarcts. In most instances in the reperfused groups the infarct was dark and hemorrhagic.

TABLE V

Velocity of Contractile Element at a Developed Pressure of 40 mm Hg

Interval (hr)	Group I	Group II	Group III
Preinfarct	1.62 ± 0.09	1.51 ± 0.12	. . .
1	1.48 ± 0.09	1.47 ± 0.11	. . .
2	1.41 ± 0.10	1.37 ± 0.09	1.59 ± 0.08
3	1.44 ± 0.10	1.31 ± 0.16	1.51 ± 0.10
5	1.39 ± 0.08	1.37 ± 0.17	1.42 ± 0.10
7	1.12 ± 0.14	. . .	1.29 ± 0.14
48	1.19 ± 0.09	. . .	1.37 ± 0.16
168	1.61 ± 0.16	1.66 ± 0.12	. . .

Velocity of contractile element (Vce) is calculated by the formula Vce = (dP/dt)/(K × IP) according to Mason et al.,[20] where dP/dt is the rate of rise of left ventricular pressure, IP is developed isovolumic pressure recorded by manometer-tipped catheter and K is the constant to obtain series elastic modulus or stiffness factor and is equal to 32. All values are in muscle lengths/sec with mean values and standard error of the mean and represent Vce calculated at a developed pressure of 40 mm Hg.

Discussion

Deleterious effects of reperfusion: The results of this study raise some important issues and contain some surprises. On the basis of the studies of Maroko et al.[15] and Ginks et al.,[16] we not only expected to find smaller infarct size and improved myocardial function with reperfusion, but also presumed that these changes would result in overall improvement of left ventricular function and better prognosis. In the group undergoing reperfusion after 2 hours of occlusion (but not in the one undergoing reperfusion after 5 hours) we did find evidence of improvement in dyskinetic and akinetic segments, but in only 42 percent; we also found smaller than expected infarcts in 50 percent of animals, but we failed to document any overall improvement. On the contrary, several deleterious effects became apparent immediately after reperfusion. Ventricular tachycardia developed almost immediately after reperfusion, even in those exhibiting reduction in dyskinesia and akinesia and a smaller infarct subsequently, and the arrhythmia invariably resulted in deterioration of overall left ventricular performance. The hemodynamic status of both reperfused groups was significantly worse 2 to 3 hours after reperfusion than that of the control group at corresponding times. In this regard, our findings are in agreement with those of Lang et al.[17] In our studies some dogs, in spite of reperfusion or indeed as

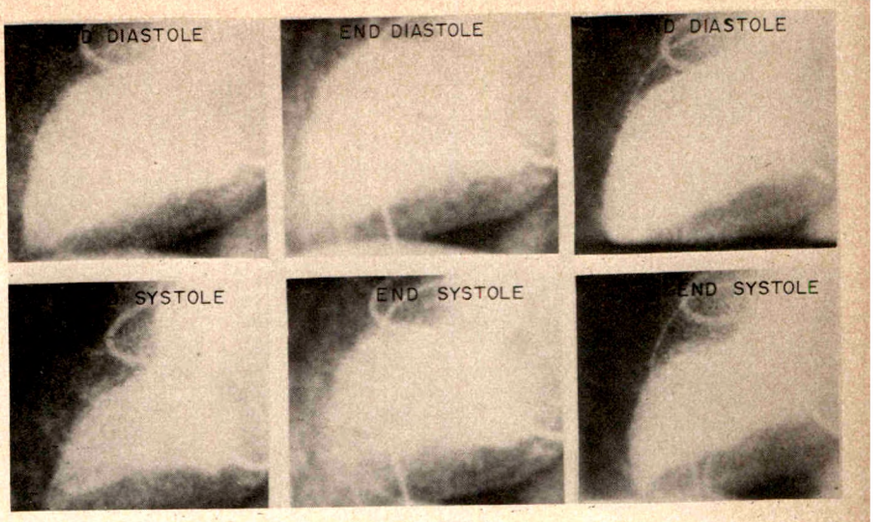

FIGURE 9. Left ventricular angiograms in left lateral projection. The **left panels** reveal a normal contractile pattern in the preinfarction state. In the **middle panels,** after coronary occlusion, marked impairment of contraction in the anterior wall is observed with dyskinesia in the anteroapical region. In the **right panels,** following reperfusion after 2 hours of occlusion, partial recovery is observed.

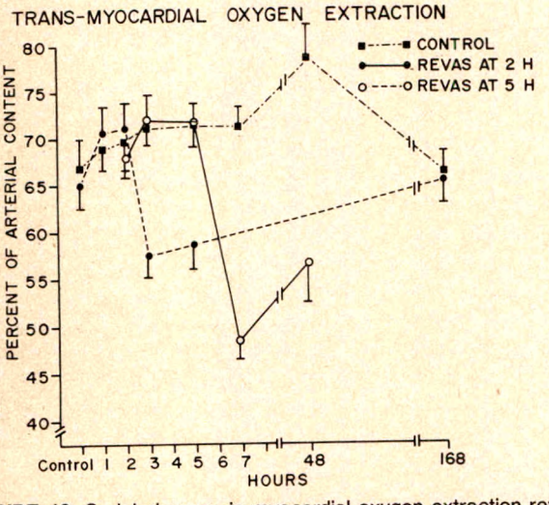

FIGURE 10. Serial changes in myocardial oxygen extraction reveal increased extraction after infarction in all groups. After revascularization (reperfusion) the level of oxygen extraction in groups II and III is acutely reduced, indicating increased blood flow due to reactive hyperemia or to nonutilization of oxygen by damaged myocardial tissues and an arteriovenous shunting effect. Findings in groups I and II are identical at 168 hours, but at 48 hours those in group III differ significantly from values in the control group ($P < 0.05$).

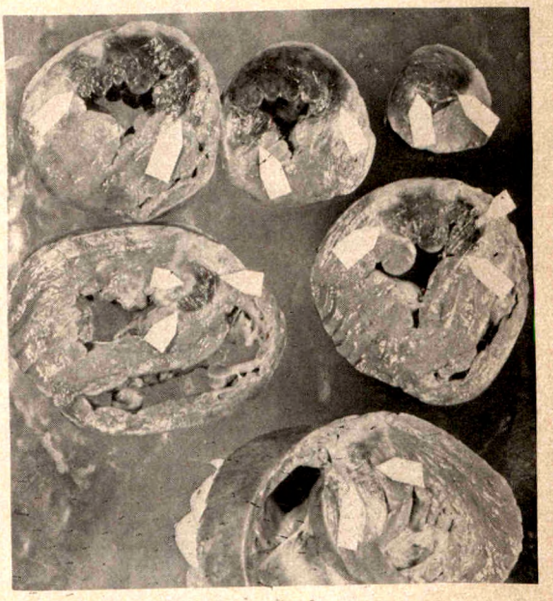

FIGURE 11. Heart of a dog subjected to reperfusion after 2 hours of coronary occlusion and killed on the 7th day. Slices have been cut transversely from the apex toward the base. A very large, dark, hemorrhagic infarcted area **(arrows)** is seen extending from the apex to the base with transmural involvement of anterior and lateral walls.

a result of reperfusion, ultimately had very large infarcts. Pathologic Q waves indicating transmural injury and infarction developed sooner in the animals undergoing reperfusion, and overall mortality was not influenced by reperfusion. Some recent studies[17,18,22] tend to support the argument that reperfusion can indeed be deleterious. It is entirely possible that in our studies the electrical instability and arrhythmias noted after reperfusion were primarily responsible for the early deterioration and that, if they had been controlled, the outcome might have been more favorable in the group undergoing reperfusion after 2 hours of occlusion.

A period of 5 hours of coronary occlusion in our model of awake dogs appears to be too long a time to expect any improvement or reversal of injury with reperfusion. Our findings are at variance with those of Bresnahan et al.,[22] who reported smaller than predicted infarct size in 9 of their 16 dogs undergoing reperfusion 5 hours after occlusion. Several others have found either irreversible injury[23–26] or only partial recovery[27] with shorter periods of occlusion.

Hemorrhagic changes after reperfusion: The development of Q waves almost immediately after reperfusion, in some dogs as early as 6 minutes, is intriguing. We have not investigated the causes of this change, but the finding of large hemorrhagic infarcts in most of these animals supports the theory recently

advanced by Bresnahan et al.[22] that reperfusion in awake animals with evolving infarction can result in extravasation of blood due to disruption of capillaries that have lost their structural integrity during the preceding period of occlusion. We found hemorrhagic infarcts, not only in those dogs reperfused after 5 hours of occlusion as did Bresnahan et al.,[22] but also in those reperfused after 2 hours. The latter finding is at variance with the results of Ginks et al.,[16] who did not report any hemorrhagic infarcts in their studies. It is not clear if the use of anesthesia in the studies of Ginks et al.[16] can account for this difference.

Determination of adequacy of coronary flow during reperfusion: One important question that must be answered in our studies, as well as those of others, is how certain are we that release of the occluding cuff, snare or other devices around the coronary artery results in true reperfusion or revascularization of ischemic and border zones. The instant development of arrhythmias with reperfusion in our studies assured us that some acute change had occurred in the affected zone, and the patency of the artery was subsequently confirmed angiographically. We realize that angiographic patency cannot be equated with adequate blood flow, and it is indeed possible that smaller capillaries had become closed off during the period of coronary occlusion in spite of administration of heparin. The angiographic appearance of arteries after reperfusion in four dogs in which the margins of the patent artery were somewhat irregular and emptying was delayed is consistent with such a possibility. Jarmakani et al.,[28] using an implanted flowmeter and external snare around the coronary artery to occlude it temporarily, were able to demonstrate return of flow, at a higher level than control level, within 15 minutes of reperfusion after 3 hours of occlusion. It is entirely possible though that structural changes in the reperfusion bed produced by 3 to 6 hours of coronary occlusion and myocardial ischemia severely limit future myocardial perfusion, even if flow is reestablished,[28,29] and that recovery may take 2 to 5 days or remain incomplete.

The demonstration of reduced myocardial oxygen extraction immediately after reperfusion in our study, as well as that of Lang et al.,[17] also indicates increased flow or reestablishment of flow. The subnormal oxygen extraction values in our studies can be explained by reflex hyperemia following a period of ischemia. The persistence of this phenomenon for 2 hours can be interpreted optimistically as indicating presence of viable tissue capable of responding by hyperemia. Alternatively, it can be explained by reduced oxygen utilization by the necrosed myocardium and production of an arteriovenous shunting effect.

Beneficial effects of reperfusion: Our interpretation that the presence of smaller infarcts in 50 percent of animals in group II suggests a possible beneficial effect of reperfusion at 2 hours may be criticized on the grounds that we compared this group with another group of animals rather than predicting infarct size in each animal before reperfusion. Such methods have been described using serum creatine phosphokinase activity[30,31] and surface mapping of S-T segment elevation.[32] The former would require a minimum of 5 hours of coronary occlusion and a suggestion has been made that the blood level of this enzyme depends not only on infarct size, but also on the perfusion and flow through involved areas.[33] The surface mapping of S-T segment elevation is a complicated technique and posed problems in our conscious dogs, which could not be kept still for such prolonged periods. We did study angiographically the movement of the ventricular wall and the extent of akinetic and dyskinetic segments. As mentioned previously, improvement after reperfusion at 2 hours was observed in 42 percent of dogs suggesting that function returned or improved in some zone of myocardium bordering necrotic or ischemic zones.

Clinical Implications

With the knowledge that infarct size can be modified in acute experimental myocardial infarction, both favorably and unfavorably,[6] and that medical revascularization using fibrinolysing agents may be beneficial in human myocardial infarction,[8–11] we attempted to study the influence of revascularization under most ideal circumstances and in a controlled manner. To achieve maximal revascularization we reperfused the occluded artery, thus restoring near normal blood flow through normal channels in dogs free of coronary atherosclerosis or other types of heart disease, within 2 to 5 hours of acute occlusion. The major difference from most previous studies was the use of intact, conscious animals and direction of observations toward the whole animal rather than portions of myocardium or some aspect of metabolism. Our studies were extended for up to 7 days. Our results indicate that if reperfusion is performed very early (2 hours after occlusion) under such ideal circumstances and noninvasively, we may indeed reduce the ultimate infarct size in some animals; however, the overall mortality remains unchanged. The process of reperfusion actually hastens the development of severe arrhythmias leading to early hemodynamic deterioration and, in many, results in immediate development of pathologic Q waves and large hemorrhagic infarcts.

We do not know the extent to which similarities with human myocardial infarction exist. Dogs have a propensity for rapid development of collateral channels, and indeed in this study, we found dramatic recovery of function within 7 days of acute infarction in the control animals that did not undergo reperfusion. Therefore, it is possible that acute reperfusion has less to offer in this species, but the fact that reperfusion is deleterious at least for a period of time in most animals is a disturbing observation. Should a similar phenomenon exist in man, acute surgical revascularization may be dangerous in the early stages of acute infarction even if in some it ultimately limits infarct

size. Such experience in acute infarction has been reported[34,35] with disastrous results, although others[12,14] have found a satisfactory outcome. Although there are definite differences between the animal model employed and patients with acute infarction, circumstances are far more favorable in our study than they are likely to be in patients with coronary disease. The ability to restore near normal blood flow noninvasively and so early in hearts that were previously normal and in which other arteries are normal is unlikely to be encountered in the course of clinical disease. If under such ideal circumstances revascularization is dangerous rather than beneficial, more studies using other species are indicated before attempting large scale surgical revascularization in the early stage of human myocardial infarction.

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Successful Partial Excision of an Intramural Fibroma of the Left Ventricle

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A report of the only surviving adult to undergo partial excision of an intramural cardiac left ventricular fibroma is presented. Good results were obtained by relieving outflow tract obstruction through partial excision of the tumor from the septum and left ventricle. The need for conservative surgical treatment of patients with this rare, benign tumor is emphasized.

Intramural fibromas of the heart are thought to comprise less than 5 percent of primary heart tumors.[1] Since the first case of fibroma of the heart was reported by Luschka[2] in 1855, more than 40 others have been reported.[3–15] This report describes successful partial resection of a massive intramural fibroma involving the posterior wall of the left ventricle and most of the interventricular septum.

Case Report

A 31 year old man first presented to the Methodist Hospital in July 1969 with the chief complaints of syncopal episodes and chest pain of 4 years' duration; the chest pain was described as dull and squeezing, followed by a sensation of dizziness. Attacks were precipitated by rapid changes in position or sudden exertion and were relieved by squatting. Past history revealed that a heart murmur was first heard at age 11 years, when a diagnosis of mitral stenosis was made. One year before admission, chest roentgenograms showed calcification in the mitral valve area.

Examination of the patient was essentially normal except for the presence of a grade 2/6 systolic ejection murmur over the entire precordium. Heart rhythm was regular and there was no detectable cardiomegaly.

Laboratory studies, including complete blood count, blood urea nitrogen, fasting blood sugar, serum electrolytes, serum lipids, uric acid and liver profile, were within normal limits. An electrocardiogram was normal except for occasional premature ventricular contractions. The chest roentgenogram revealed calcification in the area of the left ventricle and a 6.5 cm well marginated calcific lesion in the lower lobe of the right lung that was thought to be a hamartoma (Fig. 1). Chest fluoroscopy disclosed a large mass of calcium in the left ventricular wall.

A left ventricular angiogram (Fig. 2) demonstrated a calcified tubular mass arising from the free wall of the left ventricle just proximal to the aortic valve, descending on the outflow tract and projecting into it. Coronary arteriograms were normal and did not show involvement with the mass or staining in the area of mass. Left and right heart catheterization data were relatively normal, but exercise pressure data were not obtained.

Surgical findings and treatment: A preoperative diagnosis of left ventricular tumor and lower right pulmonary lobe hamartoma was made and the chest was explored through a median sternotomy on August 20, 1969. The posterior left ventricle was nodular to palpation and, on elevation of the heart, a bulky tumor could be seen in this area. Total cardiopulmonary bypass was established and the aorta cross-clamped. Through a transverse aortotomy, a large, glistening nodular mass could be seen projecting from the endocardium just inferior to the aortic valve. The mass obstructed the outflow tract, which measured approximately 1.5 cm in diameter. A left atriotomy was performed and the hard mass was palpated through the mitral valve. It

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then became apparent that the nodular calcific mass involved the entire posterior left ventricular wall and most of the interventricular septum extending just below the mitral valve to the apex; the bulk of this mass occupied approximately one half of the left ventricular cavity. A biopsy specimen was taken, a frozen section examined, and the diagnosis of benign fibroma made. The left ventricular outflow tract was cleared by excision of the nodular mass to normal myocardium where possible. Nodules extending into the left atrium were also resected. Satisfactory withdrawal of the projecting portion of the tumor from the left ventricular cavity was performed without left ventriculotomy; because of the extent of involvement, the septum and remainder of the posterior wall were left intact with some of the benign tumor remaining. The aortotomy and atriotomy were closed, and the heart was returned to a normal sinus rhythm after defibrillation. The mass in the lower lobe of the right lung was then removed by wedge resection. Diagnosis, after examination of a frozen section of the lung mass, was fibrous mesothelioma. The sternotomy was closed.

The patient's postoperative course remained uneventful and a left ventricular angiogram 1 month postoperatively revealed no outflow tract obstruction despite persistence of part of the calcified mass in the left ventricular wall. The patient has now returned to gainful employment and is asymptomatic 4 1/2 years after surgery. Permanent sections of the fibrous tumor of the left ventricle are shown in Figure 3.

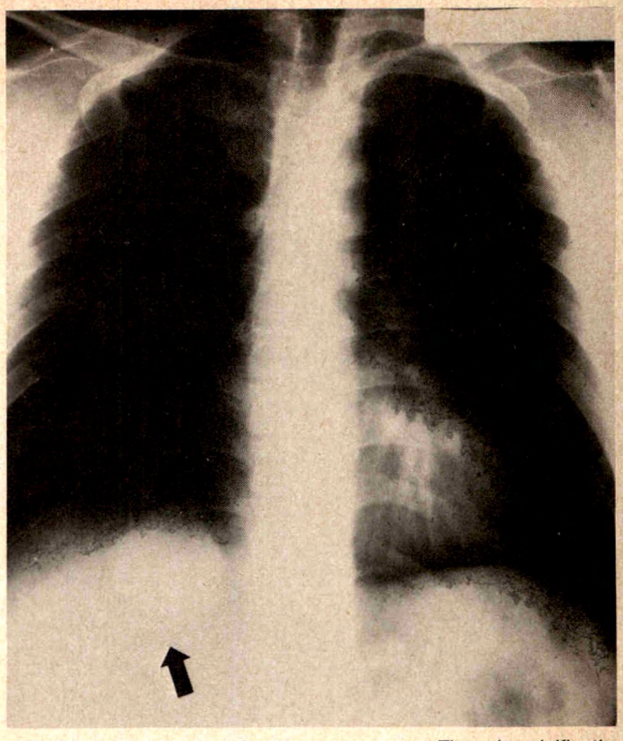

FIGURE 1. Preoperative chest roentgenogram. There is calcification in the left ventricle. **Arrow** points to a large calcified mass in the lower lobe of the right lung, later proved to be a fibrous mesothelioma of the lung.

Discussion

Patients reported to have intramural ventricular cardiac fibroma have ranged from newborns to 65 years of age but most have been children. Approximately 30 percent of the patients in previously reported cases died from "sudden death," presumably because of interference with cardiac conduction or because of outflow tract obstruction.[1]

The clinical diagnosis of intracardiac fibroma has been elusive. Findings have been confused with those of endocardial fibroelastosis[4] and pulmonary stenosis.[1] Our patient's condition was diagnosed as mitral stenosis and insufficiency for several years. Most intramural fibromas present with ventricular calcification and cardiomegaly; the final diagnosis has been made by ventriculogram, in most cases preoperatively.

Surgical excision: Because of the difficulty in diagnosis and the rarity of this tumor, only a few cases with successful surgical treatment have been reported. The first successful excision was reported by Parks et al.[3] in 1962. Their patient was a 26 month old boy with a left ventricular hamartoma composed of fibrous and cardiac muscle elements. The specimen weighed 61.5 g and calcification was present.

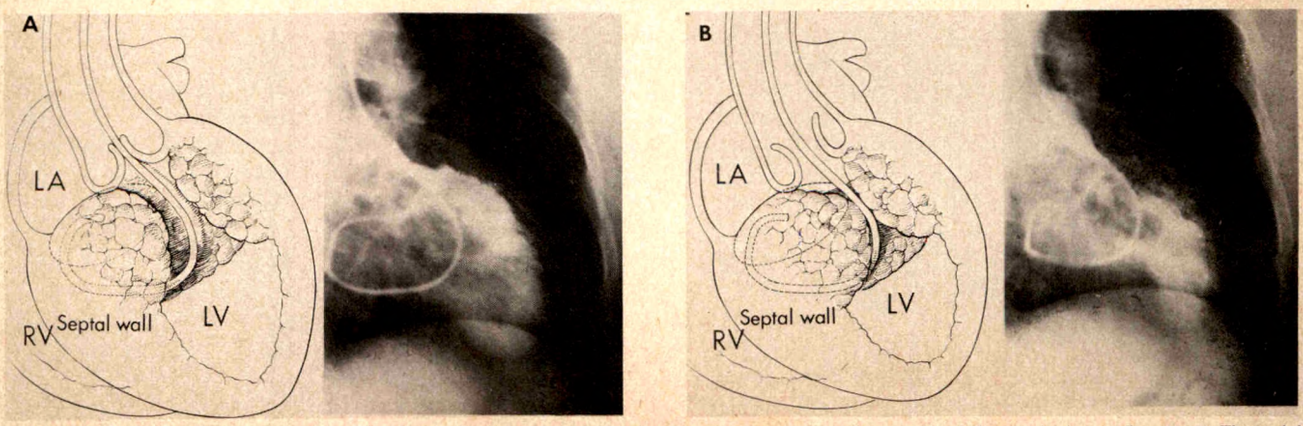

FIGURE 2. Left ventricular angiograms. **A,** during diastole, demonstrating the fibroma encroaching on the left ventricular outflow tract. The calcification can be noted in the anterior wall of the left ventricle (LV). **B,** during systole, there is further encroachment on the outflow tract. Note the large amount of calcium in the anterior wall and septum of the left ventricle.

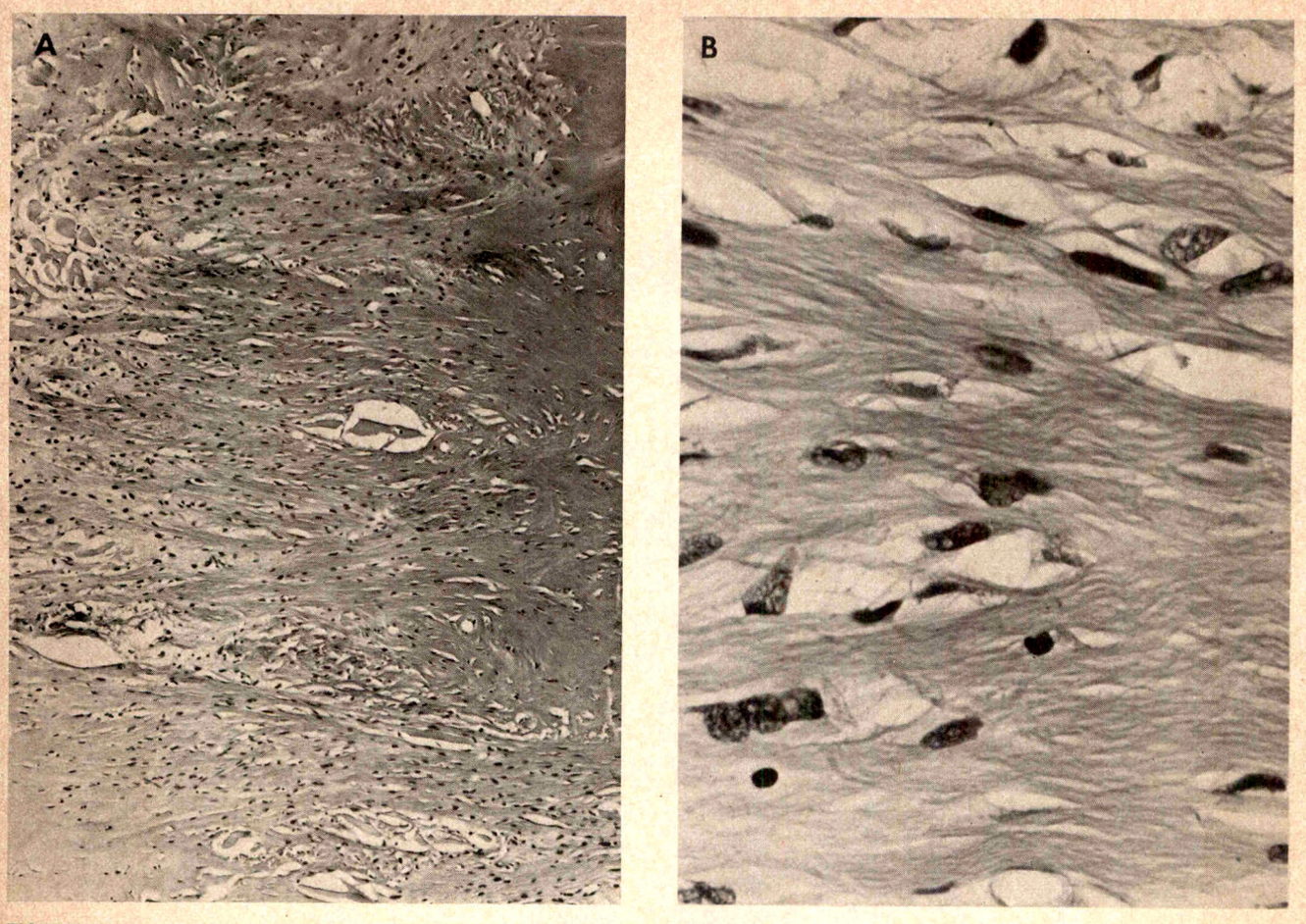

FIGURE 3. Microscopic sections of the excised tumor. **A,** the fibroma has the appearance of normal fibrous tissue with thick bundles of collagen surrounding normal fibrocytes. Note the lack of cardiac muscle. (Hematoxalin-eosin stain ×90, reduced by 25 percent.) **B,** high power view. Normal appearing fibrocytes are surrounded by large amounts of collagen. (Hematoxylin-eosin stain ×900, reduced by 25 percent.)

Excision was accomplished from the lateral and posterior aspects of the ventricular wall. The patient was followed up for 2 years and remained symptom-free.

Geha et al.[1] reported successful excision of fibroma in two children. The first, a 27 month old boy, presented with syncopal attacks and arrhythmia. A ventriculogram revealed a partly calcified intramyocardial mass. The excised mass had occupied the interventricular groove, weighed 72 g and was 6 cm in diameter. The second patient was a 38 month old boy with a systolic murmur, left ventricular calcification and cardiomegaly; a 118 g fibroma was removed from the left ventricle. Both patients apparently fared well postoperatively.

In 1968 Kay et al.[5] reported excision of an intramural fibroma of the right ventricle and interventricular septum in a 9 year old boy. The child presented with atrial tachycardia, cardiomegaly and calcification of the right ventricle; a 115 g fibroma was removed from the right ventricle and septum necessitating closure of the defect with a Teflon® patch. After 4 years of follow-up, the child was doing well despite slight calcification in the patch area.

Thomsen et al.[7] and Williams et al.[8] reported successful excision of a left ventricular fibroma in a 17 year old girl and a 30 month old boy. Hall[6] attempted resection of an extensive fibroma of the left ventricle but was unsuccessful because excision of the entire fibroma compromised left ventricular function. Thus, only partial excision is indicated in some patients.

Edlund and Holmadahl[13] were the first to make a gross surgical diagnosis of intramyocardial fibroma, discovered in the left ventricle of a 32 month old child. Valledor[14] attempted to remove an interventricular septal fibroma in an 8 month old infant, but the patient did not survive. Svejda and Tomasek[12] accomplished partial excision of a left ventricular and septal fibroma in a 17 month old infant, who did not survive.

Our patient represents the seventh successful operation for this rare condition and the first successful partial excision in an adult. Because of the biological activity of the fibroma and the extensive involvement of the left ventricle and septum, we elected to clear the outflow tract and increase left ventricular volume by excising only part of the tumor. Although it has been assumed that intramural cardiac fibromas grow by displacing myocardium, complete resection could not be accomplished in this case. Sufficient muscle mass remained to maintain good cardiac output, ade-

quate left ventricular volume, a normal conduction pattern and an unimpeded outflow tract. Moreover, the avoidance of ventriculotomy in this case preserved the remaining left ventricular muscle and its blood supply. Four years postoperatively the patient has returned to full time employment and remains symptom-free.

The incidental finding of a fibrous mesothelioma of the lung probably bears no relation to the intracardiac fibroma. T'so and Teoh[15] described a newborn infant with intramural cardiac fibroma who, at autopsy, was also found to have fibromas of the larynx and tongue and multiple fibromas of the lungs. However, these lesions were of uniform character.

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Implanted Pacemakers: Medicolegal Implications

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Cardiac pacing, which has enjoyed rapid development, is an important therapeutic tool for managing patients with cardiac dysrhythmias. The ability of muscle to respond to electrical stimulation has been known since the early experiments of Galvani, but it was not until 1952 that Zoll[1] demonstrated the feasibility of closed chest cardiac stimulation for cardiac resuscitation. Brockman et al.[2] in 1956 showed the clinical feasibility of direct electrostimulation of the myocardium in an 11 month old infant. In 1959 Furman and Schwedel[3] reported on both short- and long-term applications of transvenous cardiac stimulation in man, and in 1960 Chardack et al.[4] implanted pacemakers in patients.

Most modern artificial cardiac pacemakers are of the ventricular pacing variety, with or without sensing function, and are used to manage high degree atrioventricular (A-V) heart block; however, rapid advances in electrophysiology and pacemaker design have caused a proliferation of specialized pacemakers with many useful features for preventing or terminating cardiac dysrhythmias. An amazing fact is that most brands of marketed pacemakers are highly reliable and meet reasonable criteria for safety and fail-safe use. The industry should be commended for manufacturing such excellent devices and for maintaining superb quality control.

Although more than 200,000 patients have escaped sudden cardiac death or have had the quality of life immeasurably improved as a result of implanted pacemakers, certain areas of caution must now be acknowledged in the development and future use of these devices. The natural heart pacemakers and A-V transmission systems can fail; so too, artificial cardiac pacemakers are susceptible to battery and circuitry failure. In addition, they may slip through the net of precise quality control or may be the products of shoddy workmanship.

Areas of potential legal liability: As with any other medical or surgical procedure, implantation of cardiac pacemakers has legal implications. Segall[5] has stated that use of these devices opens up a wide area of legal liability, in tort, related to charges of malpractice against consulting or treating physicians, surgeons, hospitals and manufacturers. Malpractice charges may arise from (1) delay in reaching a decision to implant a pacemaker when implantation is clearly medically indicated; (2) failure to warn of potential complications, after effects and risks; (3) selection of a device and pacemaker system inappropriate to the patient's problem; (4) poor postimplantation care and advice; or (5) improper design or defective manufacture of the pacemaker or its impulse generator.

Other sources of possible liability include injuries due to radioactivity from nuclear-powered generators or failure to warn against pacemaker catastrophes in connection with microwave ovens, magnetic fields, radar and other possible electronic areas of interference. Liability may also be incurred when patients wearing pacemaker devices are involved in litigation resulting from automobile accidents or other areas of traumatic negligence common to the general population.

Selection of pacemakers and pacemaker failure: One important area of possible medicolegal conflict relates to the indications for and selection of pacemaker types for particular cardiac dysrhythmias. Another is a situation wherein a patient with heart disease might benefit from pacemaker implantation but a suitable device is not inserted because of inadequate or inappropriate studies and improper identification of the kind of heart disease. Undue delay in pacemaker implantation or temporary pacemaker implantation in a clinic without adequate techniques and inventory for prompt permanent pacemaker implantation and replacement may also constitute negligence. On such occasions, the need for temporary pacemaker implantation while a generator or electrodes or other connecting parts are being awaited may become urgent. During such a delay there could be dislodgment of the unit, followed by grave medical complications or even sudden death, associated with the temporary loss of pacemaker function.

Implantation of a particular type of generator without performing appropriate electrophysiologic studies may now constitute negligence on the part of the attending physician and the surgeon. One example would be the implantation of a fixed type of ventricular pacemaker in a patient who subsequently experiences return of A-V conduction and symptomatic

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competition of the pacemaker and the inherent rhythm. The implantation of pacemakers that pace the ventricles and engender retrograde conduction to the atrium (retrograde P waves either occurring at an unfavorable period in ventricular systole and causing undesirable hemodynamic results or arriving in the atrium during its vulnerable period and producing periods of atrial flutter or fibrillation) may result in legal liability on the basis of unfavorable effects.

Pacemaker monitoring: Perhaps one of the most important areas of consideration concerns adequate surveillance after implantation. Although the rate of most cardiac pacemakers decreases before battery depletion, other units may fail without perceptible warning and hence should not be monitored by the usual methods or by transtelephonic techniques. Wave form analysis can be used to determine impending pacemaker failure, but this method of surveillance is time-consuming, requires special equipment and cannot be performed by telephone. Often patients are discharged from the hospital without being given detailed information concerning the pacemaker, its life expectancy, function, type, hazards and possible complications, or, most important, precise instructions for periodic evaluation and testing of battery function. Certainly the level of sophistication of the practice will govern the surveillance system necessary for patients residing within given geographic areas. Patients who are completely pacemaker-dependent require stricter surveillance than those with comparatively minor disturbances of impulse formation and conduction. In the former, it may sometimes be wise to implant redundant pacemaker systems to protect against sudden lack of pacing, wire breakage or dislodgment since subtle problems, such as minor wire fractures or muscle action potentials, can inactivate demand-functioning pacemakers and cause sudden death.

Complications of pacemaker implantation: It is far too early to anticipate the possible long-term complications of epicardial and transvenous electrode implantation. At present, it appears that the generators themselves are safe, and we are fairly well assured that atomic units are probably also compatible with long-term safe use. However, over long periods such conditions as perforation, thrombosis, fibrosis, constriction of the superior vena cava around one or more pacemaker electrode wires, or trauma associated with attempted removal of old electrodes may entail additional risks, with consequent liability.

Every physician should be conversant with the hazards attending the failure to implant cardiac pacemakers after the development of various kinds of block within the atria, A-V node or fascicles in acute or chronic cardiac disease. The danger of sudden death must be reckoned with both in the acute phase of myocardial infarction and in the long-term clinical course of patients with residual degrees of fascicular block.

Prevention of Legal Liability

Every effort must be made to acquaint patients with the possible complications and potential hazards of pacemaker implantation. Several suggestions appear pertinent because sufficient information is now available to perform electrophysiologic studies to select the appropriate type of pacemaker and recommend postimplantation care to the patient. Failure to observe these precautions may invite legal action.

1. *Preoperative care:* The patient must sign a precise and detailed form giving informed consent. It is the affirmative duty of the physician to inform the patient and his family of the nature of the function of the pacemaker, the scope and method of implantation and the risks of complications of surgery.

2. *Intraoperative care:* A detailed record must be made on the patient's chart and identification cards issued indicating implantation date, model, electronic and electrophysiologic data, electrode threshold and recordings of demand and magnetic mode function when indicated.

3. *Postoperative care:* Since pacemakers have a natural course and are also subject to premature failure, specific recommendations concerning the responsibility for patient follow-up and the precise type of surveillance program utilizing a pacemaker clinic or transtelephonic monitoring should be prescribed before the patient is discharged from the hospital. Pacemaker manufacturers should offer patients booklets to assist them in understanding the function of the implanted unit. Patients should be warned about probable malfunction in the presence of microwave ovens, radar, radio broadcasting stations or magnetometers and should be given reassurance concerning devices that are not harmful.

Negligence as such may not be the principal legal hazard in the field of cardiac pacemakers. However, the clinician is faced with new challenges, in the form of possible suffering and reduced quality of life resulting from failure to implant a pacemaker or, conversely, from mechanical, surgical and the many electrophysiologic problems attendant upon the implantation of certain electronic circuits. The pitfalls inherent in all these situations must be recognized.

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Permanent Pacing of the Heart: A Comment on Technique

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Fixation of electrodes directly into the myocardium, the original technique for pacemaker implantation, almost disappeared from the scene for 10 years. Less than 5 percent of "pacemaker doctors" persisted in transthoracic implantation. As one might suspect, the physicians who persisted were thoracic surgeons; they argued for their method on the basis of its simplicity and swiftness and the long-term security of electrode position. Most other physicians, about one third of whom were cardiologists or internists, and two thirds surgeons, had switched to transvenous pacing because this method could be performed in patients of any age, under local anesthesia, with low operative morbidity and mortality.

Recently an interest in direct myocardial implantation was rekindled by the development of the sutureless or so-called "screw-in" electrode, and by the disclosure by some physicians that in their hands transvenous pacing was associated with a frightfully high incidence of early electrode malposition—as high as 59 percent in one report! (For the sake of brevity, malposition here includes dislodgment and ventricular perforation.) Because proponents of each technique are now figuratively toe to toe, it behooves us to evaluate the relevant arguments.

"Swiftness" and "simplicity" are characteristics that may be attributed to both methods but, one asks, swift and simple for whom? Surely transthoracic pacing would be neither swift nor simple for an internist, nor would transvenous pacing be simple or swift for every surgeon. A cardiologist, actually, could not perform a transthoracic operation, because no hospital would give him operative privileges. And yet, paradoxically, surgeons have slipped into the catheterization laboratory (because a small incision was needed?) and have been inserting transvenous pacemakers. In fact, transvenous pacing is so "simple" that many centers have given this operative responsibility to junior physicians, and sometimes to house officers.

The real issue is the problem of electrode dislodgment. Were electrodes as securely positioned with transvenous pacing as they are with transthoracic pacing, there would be no valid argument for pericardiotomy, however small the opening. Even though transthoracic pacing can be done with little morbidity and mortality, general endotracheal anesthesia is usually used (although epigastric incisions and transthoracic operations may be done under local anesthesia), the pericardium must be opened and the heart must be exposed. There are, of course, those who argue differently, but surely these factors will increase morbidity and mortality. Add to that the problem of infection, should it occur: Removal of wires by the transvenous route is a far less serious consequence than another thoracotomy. Other complications that are peculiar to transvenous pacing, such as damage to the tricuspid valve, air embolization and late perforations are not being ignored in this editorial, but they are relatively rare, and for the sake of this analysis are more than balanced by other complications that are peculiar to transthoracic pacing.

In the Inter-Society Commission for Heart Disease Resources report on pacemakers,[1] the issue of an acceptable incidence of transvenous electrode malposition was discussed. It was suggested that a figure of early dislodgment higher than 5 percent calls for a review of results by a proper audit committee (now probably PSRO), and for modification of physicians' privileges.

Our own figures for 1973 and 1974 show 9 dislodgments in 219 primary ventricular transvenous insertions (4.1 percent). A second repositioning of the 9 was never required. Perhaps this indicates that the operation could have been done better the first time! Permanent transthoracic pacing is never used at our institution except as an incidental procedure when the heart is exposed for another reason, or in rare problem situations. Since 1964 we have used the transthoracic approach five times in 1,030 complete pacemaker insertions.

Transvenous pacing can be done with only a trivial incidence of complications; it is the safest and simplest technique available. In our opinion it is the preferred pacing method in almost all situations, provided the operation is performed by a skilled physician who is *specifically trained* in the technique and all its ramifications.

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BEHAVIOR THERAPY FOR TYPE A PATIENTS

This letter briefly introduces a new approach to psychological treatment of the type A cardiac patient; fuller details will be reported later as further analyses are completed. However, some preliminary results show this approach to be promising.

The type A personality was identified by Friedman and Rosenman[1–3] in a series of well designed studies demonstrating the association of this behavioral pattern with high risk for heart disease. They also reported[3,4] that the type A traits were more predictive, with less error, of heart disease than predictions based solely upon examination of lipid data such as the beta/alpha lipoprotein level.

The type A behavioral pattern consists of: a high drive toward poorly defined goals, persistence of work toward recognition and advancement, eagerness to compete, continuous involvement in activities with self-imposed deadlines, working at such activities at a high rate, and a heightened mental and physical alertness.

The pilot program of psychological treatment was a combination of two behavior modification programs developed by Suinn[5]: anxiety management training and visuo-motor behavior rehearsal.[6] The former trains patients in identification of the physical/physiologic signs of stress and elimination of these reactions from the behavior pattern. It has been successful in patients with diffuse anxieties.[7,8] Visuo-motor behavior rehearsal is a method that enables a patient to acquire new adaptive habit patterns through practicing these patterns under controlled imagery conditions. This procedure has been applied to the retraining of executives, concert musicians and members of the United States National Ski Team.[9] The program for cardiac patients is a 5 hour treatment program called Cardiac Stress Management Training (CSMT). Patients are trained in the methods for coping with stress situations and stress arousal, and in the means for altering their lifestyles to reduce stress. It is assumed that the type A patient is particularly susceptible to stress because his behavior places him in situations of stress, for instance, from deadlines. It is also assumed that the type A patient needs to alter his activities significantly in order to avoid further stress.

All patients underwent rehabilitation in the Spalding Rehabilitation Center, Cardiac Reconditioning Unit, Denver, Colorado. This rehabilitation program is comprehensive, involving medical resources, physical exercise and dietary assistance, all individualized for each patient. Patients are introduced into the program within 2 to 4 weeks after infarction, and typically are followed up in an outpatient treatment program three times a week for 8 weeks. Blood lipid measurements are obtained at the beginning and at the end of the program through the laboratory facilities in the hospital attached to the Center.

An experimental group of 10 type A patients was selected for Cardiac Stress Management Training, with a control group of 10 who did not receive this training. All patients had been undergoing the comprehensive medical rehabilitation treatment previously indicated, that is, exercise, dietary assistance and medical supervision.

A questionnaire on the patients' reactions to the stress training program indicated that 83 percent believed it led to substantial improvements in their reactions to stress, and 83 percent believed there were major changes in their behavior patterns or lifestyles.

The median cholesterol and triglyceride levels showed, respectively, a decrease from 215 to 194 mg/100 ml and a decrease from 143 to 104 mg/100 ml in those patients who underwent the stress training. The control group showed no change in cholesterol level from the median of 214 mg/100 ml, and a decrease in triglyceride level from 146 to 130 mg/100 ml. The mean decrease in body weight in the group trained in stress management was 3.0 lb as compared with 1.3 lb for the patients in the control group. The only way in which the two groups differed was in the participation or nonparticipation in the stress management program.

Further detailed statistical analyses are being conducted on the data. At this point the stress management training program seems promising since 8 of 10 patients who participated had a decrease in cholesterol level and 9 of 10 a decrease in triglyceride level, as compared with 5 of 10 patients in the control group who had a decrease in either measurement. Since the program was developed as a short-term treatment program that can be completed in 2 weeks, it may prove to be the first meaningful approach to reducing the psychological risk factors associated with heart disease.

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COMMENT

The usual approach to management of a patient after myocardial infarction is alteration of the primary risk factors for infarction by such methods as changing diet, stopping smoking, normalizing weight, reducing serum lipids by diet and medication and enhancing physical activity, and, more recently, by purposeful programs of physical conditioning. Unfortunately, it is clear from published data that such approaches have not been associated with a significant decrease in the rate of recurring coronary events.

The association of type A behavior with the incidence of both primary and recurring coronary events seems clear from our own published data as well as the relevant data from many other investigators. The letter from Suinn et al. strongly indicates that alteration of the patient's behavior

pattern should be attempted with the hope that it may favorably influence the rate of future coronary events. Such attempts have been employed in various European centers for a number of years, and more recently in this country by Dr. Richard Rahe at the University of California at Los Angeles, and by Dr. Joseph Satten and me in our group in San Francisco, which meets twice a month for a group discussion. This behavioral approach to patient management necessarily involves a deconditioning process or a method that may enable a patient to acquire new adaptive habit patterns, as indicated by Suinn and his associates.

The preliminary results reported by Suinn et al. concerning changes in serum lipid levels in their subjects are of great interest since we have observed similar favorable responses in our own subjects after successful alterations of behavior. The low mean serum cholesterol level that Suinn et al. describe in their patients with coronary disease is surprising. However, hospitalization is usually associated with a decrease in serum lipid levels and it would be important for Suinn and his associates to compare their groups' prehospitalization serum lipid levels with the levels observed after the patients' return to usual modes of living.

I await with great interest the results of the studies of Suinn et al. and hope that their report will stimulate other investigators to conduct analogous studies with various modifications.

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RELATION BETWEEN S-T SEGMENT DEPRESSION AND S WAVE AMPLITUDE

Linhart's detailed hemodynamic measurements[1] reveal consistent reversible cardiac failure in pacing-invoked angina. We are currently investigating an electromechanical relation between the mathematically interpreted electrocardiogram and cardiac function, as described by Posel.[2,3] We have found that the amplitude of the S wave, in certain leads, can act as a left ventricular function transducer.[4,5] In this context Figure 1 of Linhart's paper[1] is particularly relevant because it demonstrates a direct relation between the left ventricular end-diastolic pressure and the S wave amplitude since they both increase in magnitude simultaneously. This apparent coincidence is also evident in Figure 1 of Linhart's previous paper.[6] The echogram in our Figure 1 reveals a clear decrease in the S wave amplitude with the reduction of left ventricular volume due to the sublingual administration of nitroglycerin.

S-T segment depression is usually associated with an increase in S wave amplitude.[7,8] Our investigations suggest that the S wave changes and the S-T depression may actually be separate though related phenomena, the S-T depression indicating anaerobism and the S wave the associated cardiac failure. We have found that during exercise the S wave changes may precede the S-T depression (Fig. 2).

Linhart has twice published reports of a relation between changes in the S wave amplitude and reversible left ventricular failure. On the basis of his published graphs and our research we expect that a review of his records from this point of view may reveal more correlations of the S wave changes with the left ventricular end-diastolic pressure changes. The accuracy of such a prediction is dependent on the use of mathematically selected leads and the absence of ventricular conduction defects. Nevertheless, we await his findings with confidence.

We believe that the possibility of an electromechanical link between the electrocardiogram and cardiac function and the implications of such a simple atraumatic monitor of cardiac hemodynamic function requires detailed investigation, particularly in the light of the detailed clinical applications described by Posel.[9]

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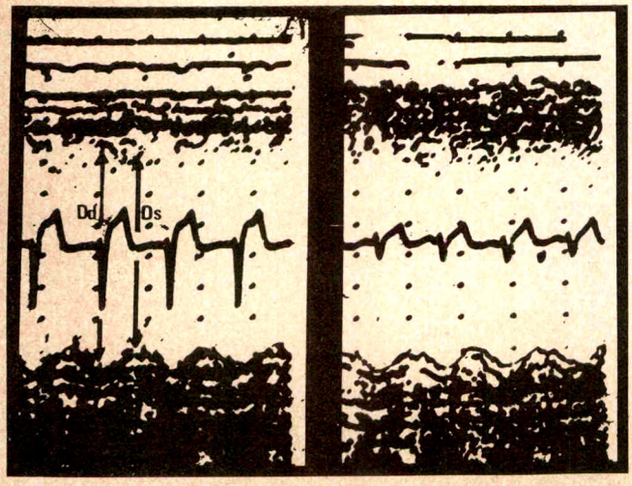

FIGURE 1. Simultaneous echocardiogram and electrocardiogram before **(left)** and after **(right)** the sublingual administration of nitroglycerin.

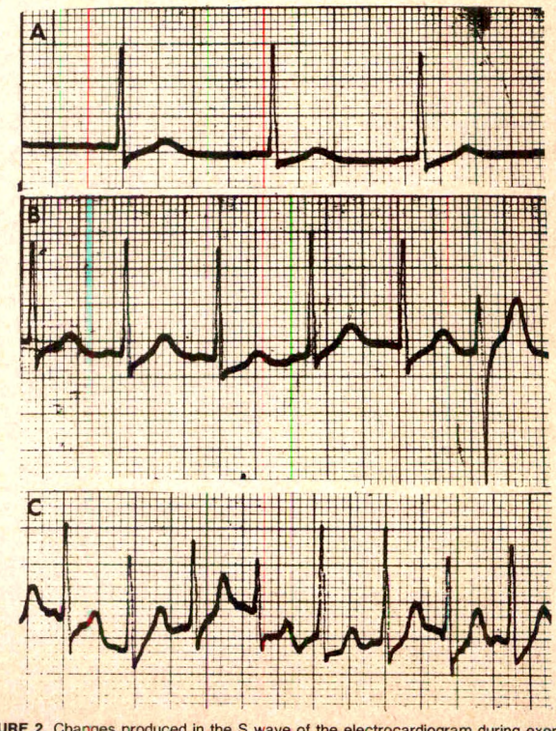

FIGURE 2. Changes produced in the S wave of the electrocardiogram during exercise. **A,** before exercise, **B,** after 1 minute of exercise at 450 kilopond meters and **C,** after 1 minute at 1050 kilopond meters.

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MAXIMAL TREADMILL TESTING

Bruce[1] recently provided convincing data on the multistage maximal treadmill test as the exercise test of first choice. This test has excellent diagnostic value in addition to providing quantitative measurement of the functional capacity of the cardiovascular system. In the prospective study reported, there was some patient selection: The average age of subjects was 45 to 52 years and most were active and working. This could explain the excellent performance and feasibility of the test (97 percent accuracy in 15,000 tests). However, the average cardiac practice contains some patients who are not always able to perform a maximal treadmill test: the elderly (±70 years), the obese, those with musculoskeletal deformities of legs or feet, or patients with claudication or sequellae of hemiparesis or hemiplegia.

It may be a question less of isometric versus dynamic tests or test X versus test Y, than of which test provides which diagnostic value or quantitative measure of cardiovascular function and is feasible not only for the patient but for the budget, time and facilities of the physician or clinic. The popularity and efficacy of the Master two-step test did not happen by coincidence.

There is now a rich variety of diagnostic tests with circulatory implications. The passive muscular tests include postural changes (from Trendelenburg position 10° to tilting [duration variable]); pharmacodynamic interventions (amyl nitrite, isoproterenol, atropine); and atrial pacing.

The active muscular tests include (1) isometric exercise (Valsalva maneuver, unilateral or bilateral handgrip or weight lifting or pushing, waterskiing [easier to study on roller skates and treadmill]); (2) dynamic exercise (walking, stepping, pedaling, jogging, running); and (3) combined isometric and dynamic exercise.

In all these tests, the same classic variables, such as heart rate, blood pressure, electrocardiographic patterns, S-T segment, dysrhythmias and symptoms and duration, are observed to assess the diagnostic value during and after testing. This wide spectrum of diagnostic tests, each with more or less severe limitations, allows most cardiologists to study most patients in most countries with a variable degree of accuracy. These tests are more supplementary than substitutive. A comparative study of most of these tests, used in the same healthy subjects and patients with coronary heart disease would be most interesting.

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REPLY

Regarding comments about ages of patients selected for a prospective study and "excellent performance and feasibility of the test," I submit the following data, updated from an earlier report,[1] comparing numbers of male patients stopped by their physicians because of unfavorable responses (numerators) with numbers of patients tested to symptomatic limits (denominators) according to 5 year age groups and clinical diagnosis before testing (Table I). All patients tested were ambulatory and none was considered to have acute or recent illness, especially myocardial infarction. The results obtained suggest both the general feasibility and the value of this method of testing to appraise cardiovascular function. In addition, there is the curious phenomenon that the majority of instances of the physician's stopping the tests occurred in healthy men under 60 years of age.

I agree that there are both multiple objectives and a variety of methods for stress testing the cardiovascular system and that many have enjoyed considerable clinical usage. As for the popular double Master two-step test, the fact that it has been used for several thousand persons does not make it the most appropriate. For example, Rowell and associates[2] pointed out the basic fallacy that, despite an effort to adjust workload in terms of steps per unit time to sex, age and weight, the test actually overtaxes the underweight patient and spares the overweight patient. Furthermore, the average oxygen requirement of 23 ml/kg of body weight per minute published by Blackburn et al.[3] happens to coincide with the average maximal oxygen uptake observed in a series of ambulatory patients with coronary disease.[4] Thus, the demand may represent 100 percent or more of the capacity in about half of patients who might be selected for testing; Master stated that patients who exhibited an unstable abnormal electrocardiogram or recent change in anginal pain at rest should not be tested, and this proved to be an important safety precaution.[5,6] A recent study from this laboratory of patients tested in the same day on both bicycle ergometers and treadmill demonstrated that on the bicycle ergometer significantly higher systemic arterial pressures and pressure-rate products were reached in the *same* patients.[7] Thus, it may be easier to overload a hypertensive or an ischemic left ventricle with this method.

TABLE I

New Data

Age Groups (yr)	Diagnoses Before Treadmill Testing				
			CHD		Prior Cardiac Arrest
	Healthy	Hypertensive	Normotensive	Hypertensive	
30–34	3/155	1/24	0/28	0/2	0/0
35–39	5/397	2/47	0/60	0/21	0/1
40–44	6/488	0/64	1/141	0/37	0/1
45–49	3/453	0/76	4/254	2/103	1/7
50–54	4/351	2/109	3/323	0/138	0/9
55–59	2/159	1/65	1/290	4/138	0/6
60–64	0/42	0/36	0/170	0/79	0/1
65–69	0/4	0/6	0/38	0/22	0/4
>70	0/1	0/8	0/11	0/2	0/1
Total	45/4426 = 1.02%				

CHD = coronary heart disease.

Bruyneel's classification of "passive muscular" diagnostic tests using changes in body posture to alter the distribution of blood volume and preload on the heart, drugs to alter peripheral resistance and myocardial contraction or pacing to alter heart rate have their place in assessing functional responses under selected conditions, but may offer less with respect to clinical diagnosis of heart disease. The isometric tests provide approaches to augmentation of ventricular afterload but, unfortunately for the patient at some risk for arrhythmias, they also evoke exercise pressor responses. Two instances are known of patients with coronary disease participating in waterskiing who experienced sudden death from ventricular fibrillation. (Although this isometric "test method" may be "easier to study on roller skates and treadmill," I seriously doubt the wisdom of having a patient with heart disease unfamiliar with this activity attempt it for the sake of making it "easier" for the observer.)

I agree that the dynamic exercises of walking, stepping, pedaling, jogging or running are better, subject to the reservations cited. For some clinical problems, it can be helpful to initiate symptoms with stressful dynamic arm exercise, either alone or in combination with limited isometric exercise. These stress tests often reveal the pathophysiologic origins of the symptoms. I also agree on the value of observations of symptoms and circulatory and electrocardiographic responses as well as the intensity and duration of exertion that elicited these responses.

As for comparative studies of physiologic responses, I suggest the papers by Doan et al.,[8] Blackburn et al.,[3] Shephard and associates (for both submaximal[9] and maximal exercise tests[10]) and Kasch et al.[11] for maximal tests in normal subjects; with respect to hemodynamic studies in hypertensive patients and those with coronary heart disease, there are additional citations.[12,13]

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BOOK REVIEWS

CARE OF THE CRITICALLY ILL, second edition, by Stephen M. Ayres, MD, Stanley Giannelli, Jr., MD and Hiltrud S. Mueller, MD. New York, Appleton-Century-Crofts, 1974, 359 pages, $12.50

This is the second edition of a book that first appeared in 1967. As Max Harry Weil mentions in the foreword, the new edition represents tangible evidence of the evolution of a new service speciality. The first edition, by Stephen Ayres, an internist, and Stanley Giannelli, a surgeon, was the first book to focus on the critically ill patient in the categorical sense. Subsequently, Centers for the Critically Ill arose and in 1970 the Society of Critical Care Medicine was organized. In 1973, the first issue of a new journal, *Critical Care Medicine,* was published under the auspices of the society. Thus, these authors set the stage for critical care medicine in concept and in name.

The present edition, like the first, was written for all concerned with the care of extremely sick people. Basic physiologic concepts are presented in Part 1; the means of applying these concepts to patients with cardiac, respiratory or renal failure, or all three, are presented in the completely rewritten Part 2. This new edition is timely, easily read, simply illustrated and useful.

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MICRO-ANGIOGRAPHY OF THE LUNG IN INFANCY AND CHILDHOOD, by Bengt Robertson, MD. Stockholm, Sweden, Proprius, 1973, 86 pages

A slim volume that offers an in-depth study of the vasculature of the lung as it evolves from fetal to neonatal and later postnatal stages, this work from a pediatric pathology laboratory utilizes a combination of microangiographic and histologic techniques to obtain a two- or three-dimensional view of the vascular bed and its interconnections and relationships. Dr. Robertson describes his findings in specimens without disease of the heart or lungs and then contrasts these "normal" findings with those obtained from babies or children who died from conditions such as the idiopathic respiratory distress syndrome or congenital heart disease. He gives details of the methodology of the injection technique and preparation of the block for X-ray exposure and stereomicroscopic analysis. Photographs of the microangiogram are displayed alongside a histologic preparation of a serial section so that the two ways of viewing the structure of the vasculature can be compared.

The author then systematically describes the pulmonary and bronchial arterial systems, the arterial bronchopulmonary anastomoses, the pulmonary and bronchial venous systems and the system of pulmonary arteriovenous anastomoses. He begins each section with a brief historical re-

view of previous workers' attempts at visualization of the different components of the vascular bed and then presents his original observations using his combined methodologic approach. Where pertinent, the author extends his anatomic observations to clinical correlates, although he is careful to point out that this postmortem demonstration of patency or communication of vessels does not necessarily imply that they functioned during life as patent or anastomosing channels. However, he reasonably states that the finding of obliterated channels can be construed to mean nonfunctional.

Examples are given of severe pulmonary stenosis or atresia wherein arterial bronchopulmonary anastomoses do not become obliterated, as is usual, but remain patent and are present in large numbers. The author likens the "pruning" of the pumonary arterial tree that is observed in roentgenograms of patients with pulmonary hypertension and vascular obstruction to the plexiform lesions he found at perpendicular branch points of the pulmonary arterial system. He also comments on the natural collateral venous path of the neonatal lung whereby true bronchial veins communicate with pulmonary veins and serve to decompress the pulmonary venous system of the neonate by draining the blood into the azygos system; this may be the explanation for the usual absence of rales in the lungs of a young baby with left-sided cardiac failure. The monograph concludes with an extensive and comprehensive list of references.

Dr. Robertson accomplishes his objective of summarizing the contributions of microangiography to the field of pulmonary vascular morphology in a way that should prove interesting and helpful to pediatric cardiologists, neonatalogists, pulmonary physiologists and pathologists.

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ADVANCES IN CARDIOLOGY: THE MYOCARDIUM, edited by Ralph Reader. Basel, Switzerland, S. Karger, 1974, 364 pages, $41.85

The proceedings of a conference on the myocardium organized by the National Heart Foundation of Australia in 1973 form the basis of the text. The presentations are by laboratory research workers and clinicians from Australia and other overseas nations who have contributed significantly to their respective areas of endeavor. The keynote address by Dr. P. I. Korner provides a succinct review of the salient points in the papers, which concern cardiac structure, excitation and conduction, contraction, muscle mechanics, myocardial metabolism, hypertrophy, coronary blood flow, clinical assessment of cardiac function, arrhythmias and coronary vein bypass surgery. The papers are well organized and the authors often present their most recent work and current theories in addition to reviewing their field of research. The photomicrographs are highly detailed, the diagrams denoting mechanisms of action are usefully designed and the presentations are selectively referenced.

This volume represents an up-to-date source of material in basic and clinical modern cardiology and will be of interest to basic researchers, clinicians and students. Although the price may reflect the inflated cost of medical research as well as devaluation of the U.S. dollar, the text is highly recommended.

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Birmingham, Alabama

MECHANISMS OF HYPERTENSION, edited by Mohinder B. Sambhi. New York, American Elsevier, 1973, 389 pages, $57.70

This volume, a record of a workshop conference on hypertension that took place in Los Angeles in 1973, is characterized by an unusually wide variation in quality, from very good to mediocre. For the internist, cardiologist or any practicing physician, the book confuses rather than clarifies the subject of hypertension. Some aspects, such as renin, angiotensin, aldosterone and prostaglandin, are overemphasized, whereas "benign" essential hypertension and its treatment are underemphasized, making much of the book irrelevant to the clinician, since 90 percent of the hypertensive patients he sees have "benign" essential hypertension. The price of the volume seems somewhat excessive since the workshop was supported by several drug companies.

The clinician will find the book confusing and unrewarding, but it will undoubtedly be of value to scientists interested in the chemistry of the hypertensive process although it contains little that is not published elsewhere.

Milton Mendlowitz, MD
New York, New York

7TH EUROPEAN CONFERENCE ON MICROCIRCULATION. PART I: METHODOLOGY ON MICROCIRCULATION, edited by J. Ditzel, MD and D. H. Lewis, MD. Basel, S. Karger, 546 pages, $104

This book comprises 80 papers presented at the 7th European Congress on Microcirculation. Part I contains a detailed explanation of methods used in the study of microcirculation and reviews the experience of internationally known pioneers in this field. The book is divided into seven chapters. The first chapter extensively discusses methods utilized for assessment of microcirculation within various organ tissues. The second deals with rheology and the influence of different physical properties of blood cells and components on microcirculation; there is a good discussion of methods and results for each study. The third chapter discusses myocardial blood flow and effects of various factors on regional coronary and collateral blood flow. The effects of intramyocardial pressure on subendocardial blood flow and the effects of clinical disease states such as left ventricular hypertrophy and acute myocardial infarction on microcirculation and coronary collateral vessels are also discussed. Other chapters deal with the use of the light microscope and electron microscope in the study of red cell agglutination and cell aggregation and general aspects of the study of microcirculation and their application in clinical states, emphasizing methods. The table of contents is somewhat limited but does not distract from the value of the book. Printing style and editing are excellent; there is sufficient information within every paper to explain its purpose, methods and conclusions.

This volume is a compendium of the study of microcirculation and is a highly specialized book of great importance to the students of this field; it is not intended for general cardiologists or clinically oriented students of cardiology. However, the highly sophisticated methods utilized and the results obtained are of value to any academician's general knowledge of microcirculation within various tissues.

Hooshang Bolooki, MD
Miami, Florida

REVIEWS IN CARDIOLOGY*

A Cooperative Program of the American College of Cardiology and the National Library of Medicine

ANEURYSM

Renal artery aneurysm. Polyaneurysmal lesion of kidney. Charron Jules, et al. **Urology** 5(1):1-11, Jan 75 (54 ref.)

ANGIOGRAPHY

Coronary arteriography. A review (first part). Johnson CD. **Bol Asoc Med PR** 65(7):158-66, Jul 73 (91 ref.)

Coronary arteriography: a review (second part). Johnson CD. **Bol Asoc Med PR** 65(10):239-45, Oct 73 (98 ref.)

AORTA

Immunologial aspects of atherosclerosis. Hollander W, et al. **Adv Cardiol** 13:192-207, 1974 (31 ref.)

ARRHYTHMIA

Electrophysiology and pharmacology of cardiac arrhythmias. V. Cardiac antiarrhythmic effects of lidocaine. Rosen MR, et al. **Am Heart J** 89(4):526-36, Apr 75 (61 ref.)

Electrophysiology and pharmacology of cardiac arrhythmias. IV. Cardiac antiarrhythmic and toxic effects of digitalis. Rosen MR, et al. **Am Heart J** 89(3):391-9, Mar 75 (44 ref.)

ARTERIES

The pathogenesis of virus-induced arterial disease--Aleutian disease and equine viral arteritis. Henson JB, et al. **Adv Cardiol** 13:183-91, 1974 (28 ref.)

Arterial wall metabolism in experimental atherosclerosis. Morrison ES, et al. **Adv Cardiol** 13:127-33, 1974 (5 ref.)

ARTERIOSCLEROSIS

Atherosclerosis in pigeons and squirrel monkeys. Bullock BC. **Adv Cardiol** 13:134-40, 1974 (26 ref.)

Immunologial aspects of atherosclerosis. Hollander W, et al. **Adv Cardiol** 13:192-207, 1974 (31 ref.)

Atherosclerosis in swine and swine as a model for the study of atherosclerosis. Luginbühl H, et al. **Adv Cardiol** 13:119-26, 1974 (32 ref.)

Genetic mechanisms in atherosclerosis. McGill, Jr HC, et al. **Adv Cardiol** 13:108-18, 1974 (39 ref.)

Arterial wall metabolism in experimental atherosclerosis. Morrison ES, et al. **Adv Cardiol** 13:127-33, 1974 (5 ref.)

Social factors and atherosclerosis. Ratcliffe HL. **Adv Cardiol** 13:141-7, 1974 (41 ref.)

Dietary fats and atherosclerosis in rat and rabbit. Renaud S. **Adv Cardiol** 13:169-82, 1974 (28 ref.)

Atherosclerosis--its pathogenesis in perspective. Wissler RW. **Adv Cardiol** 13:10-31, 1974 (95 ref.)

Lipoprotein receptors, cholesterol metabolism, and atherosclerosis. Goldstein JL, et al. **Arch Pathol** 99(4):181-4, Apr 75 (18 ref.)

ARTERIOSCLEROSIS OBLITERANS

Applications of ultrasound to the study of arteriosclerosis obliterans. Strandness DE Jr, et al. **Angiology** 26(2):187-98, Feb 75 (33 ref.)

ARTERITIS

The pathogenesis of virus-induced arterial disease--Aleutian disease and equine viral arteritis. Henson JB, et al. **Adv Cardiol** 13:183-91, 1974 (28 ref.)

BLOOD VESSELS

Atherosclerosis--its pathogenesis in perspective. Wissler RW. **Adv Cardiol** 13:10-31, 1974 (95 ref.)

CARDIAC OUTPUT

Current concepts measurement of cardiac output by thermodilution. Weisel RD, et al. **N Engl J Med** 292(13):682-4, 27 Mar 75 (6 ref.)

CARDIOVASCULAR DISEASES

Some spontaneous cardiovascular lesions in dogs and cats. Zook BC. **Adv Cardiol** 13:148-68, 1974 (56 ref.)

Drug therapy for cardiovascular disease in the aged. Kennedy RD. **J Am Geriatr Soc** 23(3):113-20, Mar 75 (20 ref.)

CARDIOVASCULAR SYSTEM

Cardiovascular dynamics: a broad view. Abelmann WH. **Adv Cardiol** 13:32-43, 1974 (17 ref.)

CAROTID ARTERIES

The modified bovine carotid artery as a vascular substitute in man. Personal experience and review of the literature. Jacobson JH 2d, et al. **Isr J Med Sci** 11(2-3):287-93, Feb-Mar 75 (36 ref.)

CORONARY DISEASE

Beta-Blockers in the management of myocardial ischemia. Davies RO. **Adv Cardiol** 13:315-29, 1974 (92 ref.)

Genetic mechanisms in atherosclerosis. McGill, Jr HC, et al. **Adv Cardiol** 13:108-18, 1974 (39 ref.)

Social factors and atherosclerosis. Ratcliffe HL. **Adv Cardiol** 13:141-7, 1974 (41 ref.)

Exercise training in the treatment of coronary heart disease. Mitchell JH. **Adv Intern Med** 20:249-72, 1975 (85 ref.)

Coronary arteriography: a review (second part). Johnson CD. **Bol Asoc Med PR** 65(10):239-45, Oct 73 (98 ref.)

Coronary arteriography. A review (first part). Johnson CD. **Bol Asoc Med PR** 65(7):158-66, Jul 73 (91 ref.)

Factors influencing infarct size following coronary artery occlusion. Kjekshus JK. **J Oslo City Hosp** 24(11-12):155-75, Nov-Dec 74 (80 ref.)

CORONARY VESSELS

Pathologic aspects of the idiopathic cardiomyopathies. Roberts WC, et al. **Adv Cardiol** 13:349-67, 1974 (17 ref.)

DIGITALIS GLYCOSIDES

Electrophysiology and pharmacology of cardiac arrhythmias. IV. Cardiac antiarrhythmic and toxic effects of digitalis. Rosen MR, et al. **Am Heart J** 89(3):391-9, Mar 75 (44 ref.)

Digitalis in acute myocardial infarction: help or hazard? Rahimtoola SH, et al. **Ann Intern Med** 82(2):234-40, Feb 75 (88 ref.)

ELECTROCARDIOGRAPHY

Developmental electrocardiography in inbred perinatal hamsters. Laird CW. **Adv Cardiol** 13:250-69, 1974 (19 ref.)

The interpretation of electrocardiograms in small animals. Darke PGG. **J Small Anim Pract** 15(9):537-52, Sep 74 (33 ref.)

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* Citations obtained from the National Library of Medicine's MEDLARS Retrieval Program—Bibliography of Medical Reviews. The first of these Bibliographies, and an explanatory editorial, appeared in the September 1971 issue (Am J Cardiol 28: 366–367, 1971).

ENDOCARDIUM

Pathologic aspects of the idiopathic cardiomyopathies. Roberts WC, et al. **Adv Cardiol** 13:349-67, 1974 (17 ref.)

EXERCISE THERAPY

Exercise training in the treatment of coronary heart disease. Mitchell JH. **Adv Intern Med** 20:249-72, 1975 (85 ref.)

HEART

Cardiovascular dynamics: a broad view. Abelmann WH. **Adv Cardiol** 13:32-43, 1974 (17 ref.)

Developmental electrocardiography in inbred perinatal hamsters. Laird CW. **Adv Cardiol** 13:250-69, 1974 (19 ref.)

Stanford cardiac transplantation. A review. Dong E Jr, et al. **Isr J Med Sci** 11(2-3):264-7, Feb-Mar 75 (10 ref.)

HEART BLOCK

Atrioventricular block (first of two parts). Kastor JA. **N Engl J Med** 292(9):462-5, 27 Feb 75 (25 ref.)

HEART CONDUCTION SYSTEM

Electrophysiology and pharmacology of cardiac arrhythmias. V. Cardiac antiarrhythmic effects of lidocaine. Rosen MR, et al. **Am Heart J** 89(4):526-36, Apr 75 (61 ref.)

HEART DEFECTS, CONGENITAL

Pathologic and genetic studies of congenital heart disease in the dog. Patterson DF. **Adv Cardiol** 13:210-49, 1974 (30 ref.)

Current status of the surgical treatment of truncus arteriosus. Poirier RA, et al. **J Thorac Cardiovasc Surg** 69(2):169-82, Feb 75 (48 ref.)

HEART DISEASES

Cardiovascular dynamics: a broad view. Abelmann WH. **Adv Cardiol** 13:32-43, 1974 (17 ref.)

HEART RATE

Developmental electrocardiography in inbred perinatal hamsters. Laird CW. **Adv Cardiol** 13:250-69, 1974 (19 ref.)

HEART VALVE DISEASES

Echocardiography in valvular heart disease. Teichholz LE. **Prog Cardiovasc Dis** 17(4):283-302, Jan-Feb 75 (140 ref.)

HYPERTENSION

Abnormal regulation of aldosterone in hypertension. Luetscher JA, et al. **Adv Intern Med** 20:183-96, 1975 (27 ref.)

Renal vascular tone in essential and secondary hypertension: hemodynamic and angiographic responses to vasodilators. Hollenberg NK, et al. **Medicine (Baltimore)** 54(1):29-44, Jan 75 (71 ref.)

HYPERTENSION, RENAL

The renin axis and vasoconstriction volume analysis for understanding and treating renovascular and renal hypertension. Laragh JH, et al. **Am J Med** 58(1):4-13, Jan 75 (39 ref.)

Malignant hypertension. Reubi E. **Clin Nephrol** 2(6):211-4, Nov-Dec 74 (36 ref.)

LYMPHATIC SYSTEM

Lymphoreticular infiltration in human tumours: prognostic and biological implications: a review. Underwood JC. **Br J Cancer** 30(6):538-48, Dec 74 (104 ref.)

MYOCARDIAL DEPRESSANTS

Electrophysiology and pharmacology of cardiac arrhythmias. V. Cardiac antiarrhythmic effects of lidocaine. Rosen MR, et al. **Am Heart J** 89(4):526-36, Apr 75 (61 ref.)

MYOCARDIAL DISEASES, PRIMARY

Molecular abnormalities in cardiomyopathy. Dhalla NS, et al. **Adv Cardiol** 13:282-300, 1974 (28 ref.)

Pathologic and genetic studies of congenital heart disease in the dog. Patterson DF. **Adv Cardiol** 13:210-49, 1974 (30 ref.)

Pathologic aspects of the idiopathic cardiomyopathies. Roberts WC, et al. **Adv Cardiol** 13:349-67, 1974 (17 ref.)

MYOCARDIAL INFARCT

Advances in cardiovascular techniques now suitable for use in the coronary care unit of the community hospital. Rackley CE. **Ala J Med Sci** 2(3):181-6, Jul 74 (5 ref.)

Digitalis in acute myocardial infarction: help or hazard? Rahimtoola SH, et al. **Ann Intern Med** 82(2):234-40, Feb 75 (88 ref.)

Factors influencing infarct size following coronary artery occlusion. Kjekshus JK. **J Oslo City Hosp** 24(11-12):155-75, Nov-Dec 74 (80 ref.)

MYOCARDITIS

Viral myocarditis in animals. Gainer JH. **Adv Cardiol** 13:94-105, 1974 (68 ref.)

MYOCARDIUM

Drug-induced cardiomyopathies. Buja LM, et al. **Adv Cardiol** 13:330-48, 1974 (36 ref.)

Molecular abnormalities in cardiomyopathy. Dhalla NS, et al. **Adv Cardiol** 13:282-300, 1974 (28 ref.)

Pathologic aspects of the idiopathic cardiomyopathies. Roberts WC, et al. **Adv Cardiol** 13:349-67, 1974 (17 ref.)

PULMONARY ARTERY

Current status of the surgical treatment of truncus arteriosus. Poirier RA, et al. **J Thorac Cardiovasc Surg** 69(2):169-82, Feb 75 (48 ref.)

VASODILATOR AGENTS

Renal vascular tone in essential and secondary hypertension: hemodynamic and angiographic responses to vasodilators. Hollenberg NK, et al. **Medicine (Baltimore)** 54(1):29-44, Jan 75 (71 ref.)

VASOMOTOR SYSTEM

The renin axis and vasoconstriction volume analysis for understanding and treating renovascular and renal hypertension. Laragh JH, et al. **Am J Med** 58(1):4-13, Jan 75 (39 ref.)

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

1975

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

SEPT. 8–9 — **Stress Electrocardiography.** Borys Surawicz, FACC, and Paul L. McHenry, FACC, directors. University of Kentucky Medical Center, Lexington, Ky.

SEPT. 22–26 — **Core Curriculum: Mechanisms and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC, director and Albert N. Brest, FACC and Yoshio Watanabe, FACC, co-directors. The Lankenau Hospital, Philadelphia, Pa.

SEPT. 30–OCT. 2 — **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya and James C. Dillon, FACC, co-directors. Indianapolis Hilton Hotel, Indianapolis, Ind.

OCT. 6–15 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. University of Missouri—Kansas City School of Medicine, Kansas City, Mo.

OCT. 8–9 — **Louis N. Katz Symposium—Coronary Artery Disease 1975: Dilemma, Dialogue and Decision.** Sylvan Weinberg, FACC, Leonard S. Dreifus, FACC, Herman Hellerstein, FACC, directors and Homer D. Cassel, FACC, honorary program director. Good Samaritan Hospital, Dayton, Ohio

OCT. 9–11 — **New Techniques and Concepts in Cardiology: Pathogenesis, Diagnosis and Treatment of Coronary Atherosclerosis.** Stephen E. Epstein, FACC, director. Washington Hilton Hotel, Washington, D.C.

OCT. 14–16 — **Ischemic Heart Disease: Current Concepts.** William J. Grace, FACC, director and Richard J. Kennedy, FACC and James T. Mazzara, FACC, co-directors. St. Vincent's Hospital and Medical Center of New York, New York, N.Y.

NOV. 6–8 — **Core Curriculum: Phonocardiography and Pulse Recording—Workshop.** Morton E. Tavel, FACC, director. The Methodist Hospital Graduate Medical Center, Indianapolis, Ind.

NOV. 12–14 — **Core Curriculum: Echocardiography, Phonocardiography and Pulse Tracings—A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

DEC. 7–9 — **Advances in Heart Disease 1976.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, Calif.

DEC. 7–10 — **Structure—Function Correlations in Cardiovascular Disease.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, Va.

DEC. 10 — **Colloquia in Cardiology—Number 8: Stress and the Heart: The Influence and Management of Stress in Heart Disease.** Robert W. Oblath, FACC and Ronald Danzig, FACC, directors. Ambassador Hotel, Los Angeles, Calif.

DEC. 12–14 — **The Dwight E. Harken Symposium: Advances in the Prophylaxis and Therapy of Cardiovascular Disease.** Henry I. Russek, FACC, director. Americana Hotel, New York, N.Y.

1976

JAN. 11–13 — **Future Directions in the Management of Cardiac Disease: A Bicentennial Viewpoint.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC and James S. Forrester, co-directors. Snowmass-at-Aspen, Aspen, Colo.

JAN. 19–22 — **Core Curriculum: Pediatric Echocardiography.** Richard A. Meyer, director and Samuel Kaplan, FACC, co-director. Children's Hospital, Cincinnati, Ohio

FEB. 23–26 — **Twenty-fifth Annual Scientific Session.** Charles Fisch, FACC, president. Marriott Motor Hotel, New Orleans, La.

NEW MEMBERS

The following individuals were elected to membership in the American College of Cardiology on May 22, 1975, in the category indicated.

FELLOWSHIP

ADES, Felix, MD, Massachusetts
ADYANTHAYA, Ajit V., MD, Texas
AKER, Umit T., MD, Missouri
AKHTAR, Abdul H., MD, Pakistan
ANDERSON, Terence W., BM, Ontario
ARTHUR, Arvin, MD, Kansas
ASKANAS, Aleksander, MD, New York
AVENTURA, Avenilo P., MD, Philippines
BAKER, Lawrence D., MD, Massachusetts
BAKSI, Kanti B., MD, India
BASTA, Lofty L., MD, Oklahoma
BHATIA, Madan L., MB, India
BLOCK, Peter C., MD, Massachusetts
BOZEMAN, James R., MD, Louisiana
BUDOW, Jack, MD, New York
BUJA, Louis M., MD, Texas
CARLINER, Nathan H., MD, Georgia
CHOPRA, P. S., MD, Wisconsin
DeCRINIS, Kurt A., MD, California
DIACO, Nicholas V., MD, California
EARNEST, James B., MD, Missouri
EL-SHERIF, A. A., MD, Egypt
FINEGAN, Robert E., MD, California
FISHER, Elizabeth A., MD, Illinois
FITZGERALD, Joseph C., MD, Maryland
FLINT, James F., MD, Connecticut
FRIEDLAND, Sigmund W., MD, Texas
GANGULY, Sunilendu N., MD, Michigan
GARCIA-Cornejo, Marcelo, MD, Mexico
GESELOWITZ, David B., PhD, Pennsylvania
GILMORE, Joseph P., PhD, Nebraska
GOLDEN, Michael S., MD, Washington
GORDON, Fallon T., MD, Texas
GUNDEL, Walter D., MD, Vermont
GWYNN, Robert E., MD, California
HAMILTON, John R., III, MD, California
HARRIS, Jackson, MD, Tennessee
HAWLEY, William D., MD, Oklahoma
HECKMAN, Aldred A., Jr., MD, Texas
HEIDENREICH, Fred P., MD, Pennsylvania
HOPKINS, F. Thomas, MD, Pennsylvania
HORN, Howard R., MD, Tennessee
HUNG, Jui-Sung, MD, Minnesota
KLAUS, Andrew P., MD, Ohio
KLOSTER, Frank E., MD, Oregon
KORNREICH, Fred, MD, Belgium
KRONCKE, George M., MD, Wisconsin
LEVY, Samuel, MD, France
LIEN, Wen-Pin, MD, Taiwan
LIGHTFOOT, Paul R., MD, California
LOOP, Floyd D., MD, Ohio
LUE, Hung-Chi, MD, Taiwan
McGOUGH, Edwin C., MD, Utah
McLAURIN, Lambert P., MD, North Carolina
MARTIN, Robert G., MD, Alabama
MATTERN, Allan L., MD, California
MATTOX, Kenneth L., MD, Texas
MAYES, Charles E., MD, North Carolina
MEHROTRA, P. P., MD, Washington, D. C.
METZGER, Clyde C., MD, Ohio
MILAM, John D., MD, Texas
MOOKHERJEE, Saktipada, MD, New York
MORRIS, Clifton T., Jr., MD, Louisiana
MORRIS, Stephen N., MD, Indiana
MOUSER, Lowell T., MD, Washington
MURPHY, David A., MD, Nova Scotia
NAIK, B. K., MB, India
NATARAJAN, Ponnuswamy, MD, Massachusetts
ORDUBADI, M. Hossein, MD, Iran
OURY, James H., MD, California
PANDEY, Mrigendra Raj, MB, Nepal
PATTON, Robert M., MD, Louisiana
PEAK, Howard J., MD, Australia
PEREZ-Anzalota, Jose R., MD, Puerto Rico
PFEIFER, James F., MD, California
PHORNPHUTKUL, Charlie, MD, Thailand
ROBERTS, Jay, PhD, Pennsylvania
ROGAL, Philip J., MD, New York
ROSENQUIST, Glenn C., MD, Maryland
RYAN, Joseph M., MD, Ohio
SAVITZ, Saul P., MD, California
SCHILLER, Nelson B., MD, California
SCHNITZLER, Robert N., MD, Texas
SHAW, David J., MD, California
SHAY, Sujint S., MD, Illinois
SHERMAN, Joel A., MD, Connecticut
SILVER, Arthur W., MD, California
SUKUMAR, Israel P., MD, India
SUNDERLAND, Cecille O., MD, Oregon
SURYAPRASAD, Agaram G., MD, Ohio
THOMAS, Dean E., M.D., Illinois
VAN REMOORTERE, Emile C., MD, Nevada
VAUGHAN, Michael S., MD, Pennsylvania
VINCENT, G. Michael, MD, Utah
YEAGER, Rodric M., MD, Louisiana
ZAMUDIO, Fernando A., MD, California
ZOLLER, Robert P., MD, Oklahoma

ADVANCE TO FELLOWSHIP

ACIERNO, Louis J., MD, New York
BOWERS, John A., MD, Nevada
CAHUE, Antonio, MD, Florida
CAMPBELL, W. Barton, MD, Tennessee
COHEN, George H., MD, California
COHEN, Howard C., MD, Illinois
ENTMAN, Mark L., MD, Texas
FIEDOTIN, Arnoldo, MD, Georgia
FISHENFELD, Jaco, MD, California
GOODMAN, Mark A., MD, New York
GUIHA, Nabil H., MD, Pennsylvania
HAAS, John M., MD, Washington
HAGAN, Arthur D., MD, California
HAIAT, Robert, MD, France
LUBELL, David L., MD, New York
NARULA, Onkar S., MD, Florida
PLOTT, Michael F., MD, Maryland
RUBENFIRE, Melvyn, MD, Michigan
SMITH, McKamy, MD, Mississippi
SMITH, Roger E., MD, North Carolina
SPICER, Melvin J., MD, Texas
SPRING, Donald A., MD, Wisconsin
STANLEY, Alfred W. H., Jr., MD, Alabama
VANSTROM, Neal R., MD, California
WITTNER, Richard S., MD, California
WOLF, Robert E., MD, New York

ASSOCIATE FELLOWSHIP

AGHA, Abdul S., MD, Florida
AHMAD, Masood, MD, Missouri
AHMED, Syed A., MD, Missouri
BREAUX, Patrick C., MD, Louisiana
CAUDILL, Christopher C., MD, Nebraska
CINTRON, Guillermo B., MD, Puerto Rico
* CORYA, Betty C., MD, Indiana
DeSILVEY, Dennis, MD, New Jersey
FELNER, Joel M., MD, Georgia
FLEISHER, James H., MD, California
HASTILLO, Andrea, MD, Virginia
KERIN, Nicholas, MD, Ohio
KHAN, Ashfaque A., MD, Illinois
* KHOO, Kah Lin, MBBS, Malaysia
LEE, Cheng-Chong, MD, Michigan
LUCIA, Walter, MD, Connecticut
MATHEW, Puthenpurakal K., MD, New York
MAYLARD, John B., MD, California
MEHTA, Arunkumar N., MD, Michigan
MISPIRETA-Vargas, Jorge L., MD, Mexico
MOODY, Carroll L., MD, Florida
MOOTHART, Richard W., MD, Colorado
MORGANROTH, Joel, MD, Pennsylvania
* NAMIN, Ernesto P., MD, Philippines
OKOROMA, Edwin O., MD, Nigeria
POOLE, Pierre P., MD, Texas
† SATINSKY, Jonathan D., MD, Pennsylvania
SCAMPARDONIS, Gregory J., MD, Greece
SESTIER, Francois, MD, Quebec
† STIMMEL, Barry, MD, New York
TUCKER, Stanley C., MD, Virginia
‡ URRUTIA, Luis E., MD, San Salvador
VAWTER, Michael H., MD, Arizona
WALINSKY, Paul, MD, Pennsylvania
¶ WOOD, Donald M., MD, Maryland

ADVANCE TO ASSOCIATE FELLOW

ESPINOZA, Jaime, MD, Peru
* JOHNSON, Jerome L., MD, California
LONDON, Anthony R., MD, New York
LOZANO, Jose R., MD, Venezuela
RODRIGUEZ, Gaston R., MD, Mississippi
* THOMPSON, Audrey J., MD, Arkansas
* TORRES, Ludgerio D., MD, Philippines

AFFILIATE

* ALLISON, A. Reid, Jr., MD, Pennsylvania
AYNESWORTH, M. Brian, Jr., MD, Texas
* BIBERMAN, Leonard, MD, New York
BLAU, Nathan, MD, Delaware
CHUGHTAI, Abdul L., MD, New York
* CONLON, Donald J., MD, California
DAVIS, David H., MD, Missouri
Del PRETTE-Lissot, Alberto, MD, Venezuela

* DUNCAN, Jackson T., Jr., MD, South Carolina
HA, Din, MD, South Viet Nam
HARKEN, Alden H., MD, Washington, D. C.
KENCHANAGOWDRA, S., MD, Missouri
* LOURIDAS, George, MD, Greece
McGUIRE, Michael R., MD, Kansas
* MANFROI, Waldomiro C., MD, New York
MATHEY, Detlef G., MD, California
MRACEK, James R., MD, Alabama
MURPHY, Barry L., MD, Kansas
POLINER, Lawrence R., MD, Texas
ROPER, Philip A., MD, Arizona
SHOROFSKY, Morris A., MD, New York
* SU, Shyh-Min, MD, Pennsylvania
* SUSSER, David, DO, Michigan
TOEWS, Warren H., MD, Colorado
WOHL, Armand J., MD, Texas
YEOMAN, Mark A., MD, Texas
YOUNG, Raymond A., MD, Georgia
ZAFAR, Muhammad I., MD, Florida

* Elected December 30, 1974
† Elected April 25, 1974
‡ Elected July 18, 1974
¶ Elected October 15, 1974

CANDIDATES CERTIFIED

Candidates Certified by the Subspecialty Board on Cardiovascular Disease American Board of Internal Medicine 1975

January through February

Masud Ahmad
Portland, Ore.

Richard D. Biggs, Jr.
Baltimore, Md.

Daniel J. Bleifer
Beverly Hills, Calif.

James P. Christodoulou
New York, N. Y.

Renato Cutarelli
Cleveland, Ohio

James C. Dangel
Sudbury, Mass.

Luis De Carvalho
Pleasanton, Calif.

Rosario L. DiBernardo
Oxnard, Calif.

D. Angus Duncan
Portland, Ore.

William B. Dunkman
Philadelphia, Pa.

Peter M. Duvoisin
Chattanooga, Tenn.

Ernest E. Federici
Westfield, N. J.

Sidney Fenig
Great Neck, N. Y.

Arnoldo Fiedotin
Atlanta, Ga.

James S. Forrester
Los Angeles, Calif.

Oscar B. Garfein
New York, N. Y.

Samuel Gray, III
Natrona Heights, Pa.

Joseph G. Hayes
New York, N. Y.

Fred P. Heidenreich
Lower Burrell, Pa.

Richard H. Helfant
Philadelphia, Pa.

John A. Kiely
Ft. Meade, Md.

Stanley M. Kleinman
Los Angeles, Calif.

Susan A. Kline
Southport, Conn.

Joel Kupersmith
Bronxville, N. Y.

Stanley V. Leblang
New Rochelle, N. Y.

James C. McFarland
Cambridge, Mass.

Nasser Nabi
Milton, Mass.

Robert I. Nacht
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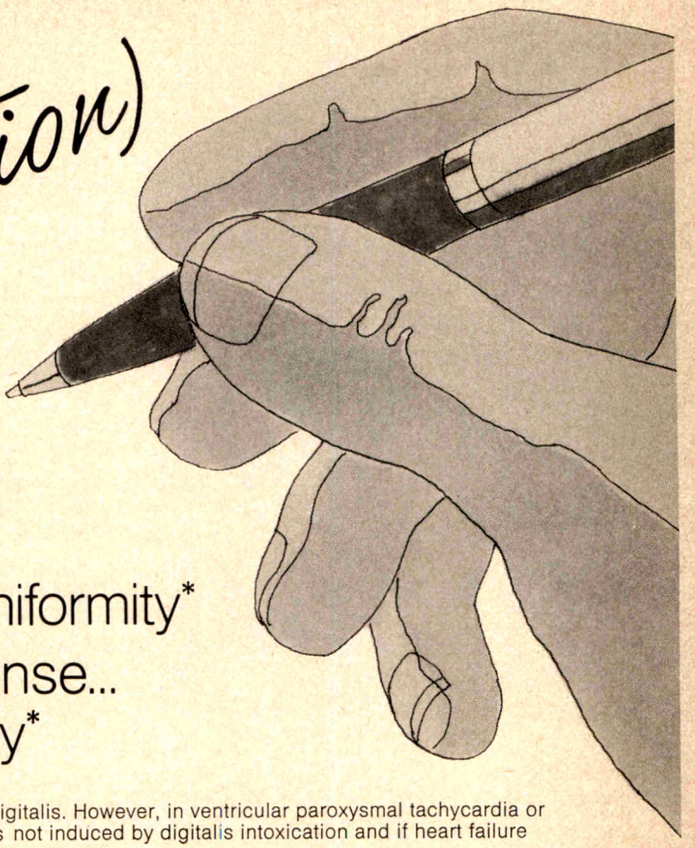
(no substitution)



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precision quality control...
- assured tablet content uniformity*

predictable patient response...
- proven biologic availability*

Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

LANOXIN® digoxin TABLETS. **0.125 mg.** (yellow) in bottles of 100 and 1,000. **0.25 mg.** (white) scored, in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack, strips of 10 tablets, 10 boxes of 100 tablets (1,000). **0.5 mg.** (green) scored, in bottles of 100 and 1,000.

Lanoxin® digoxin

*Complete literature available on request from Professional Services Dept. PML.

Wellcome

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Research Triangle Park
North Carolina 27709

Principles of oral anticoagulation

Practical Considerations

Identifying your patient at risk of thromboembolic complications

While every MI patient is not a candidate for oral anticoagulation therapy, a history of previous infarct or angina, persistent atrial fibrillation or congestive failure, severe hypotension or shock or serious arrhythmia may increase risk of thromboembolic complications.

In addition, certain procedures often place your surgical patient, particularly if he's over 40 years of age, in the high risk category—cup arthroplasty or pelvic surgery, heart valve replacement, reparative vascular surgery.

Your geriatric patient, too, is at high risk of thromboembolism if he's suffered a fracture—especially of the hip, pelvis or a lower extremity—or if his history includes venous insufficiency.

For any of these individuals, obesity, previous episodes of venous thrombosis or pulmonary embolism and a future including prolonged bed rest all increase the risk of thromboembolic complications, and make him a candidate for oral anticoagulation.

Laboratory monitoring

For every patient receiving COUMADIN® (*crystalline* sodium warfarin), frequent laboratory monitoring is a key to effective therapy. Determine prothrombin time daily until results stabilize in the therapeutic range —1½ to 2½ times normal. Individualize dosage and administration as indicated by prothrombin time results. Determine subsequent prothrombin times periodically throughout the course of therapy.

Educating your patient

Because a patient is generally more reliable if he understands his condition and his medication, he should be made aware of the factors that may influence his prothrombin time and, therefore, his response to COUMADIN®—dietary change, travel, other medication, change in physical condition and abrupt environmental change. What's more, he should know the importance of regularly taking the exact dosage of COUMADIN® prescribed and of keeping every appointment with you and with the laboratory.

COUMADIN® is an Endo U.S. registered trademark.

Therapeutic principles put into practice

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional and lumbar block anesthesia.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Pregnancy–COUMADIN® passes through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage **in utero,** even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. The newborn may be particularly sensitive to sodium warfarin. There have been reports of birth malformations in children born to mothers who have been treated with warfarin during the first trimester of pregnancy. Whether warfarin was in fact the responsible agent has not been established. Therefore, women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed. If COUMADIN® must be used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks. **Lactation**–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Spinal puncture. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN® , thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN® .

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methylphenidate; monoamine oxidase inhibitors; nalidixic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates (in excess of 1 Gm/day); sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN® . Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K-dependent factors, namely Factors VII, IX, X and II, the factors affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN . The initial dose of heparin and injectable COUMADIN may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time; and therefore, when patients are receiving both heparin and COUMADIN® , the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN® may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Water for Injection. 75 mg: Unit consists of 1 vial, 75 mg; sodium chloride, 15 mg; thimerosal, 0.3 mg. pH is adjusted with sodium hydroxide, accompanied by a 3 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

Rev. April, 1975

*Present as crystalline sodium warfarin isopropanol clathrate.

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EDO-2620

DUPONT

This is the heart of the new CardioBeeper® system.
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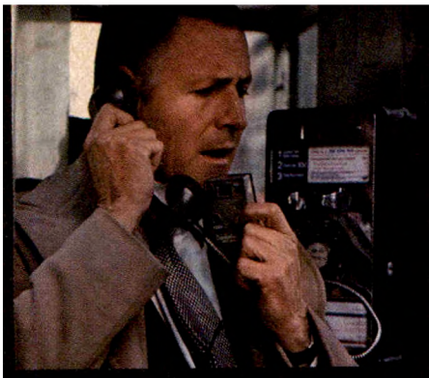
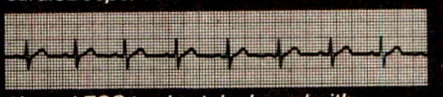
It can change your concept of patient care.



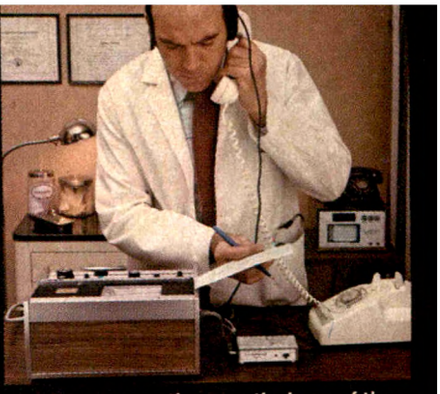
The CardioBeeper® heart monitor and CardioBeeper®-PM pacer monitor are unlike any heart monitoring instruments now in use. They're five ounces, pocket-sized and relatively inexpensive. Yet they are unparalleled in electronic sophistication. The CardioBeeper monitors are engineered to permit your coronary patient, within seconds, to telephonically transmit his heart rate and rhythm or ECG. And to allow your pacemaker patient to transmit pacemaker rate interval and artifact, as well as confirmation of battery integrity and ventricular capture. At any time. From any conventional telephone. If indicated, you are then able to institute immediate, often life-sustaining action.

Pacemaker tracing telephoned with CardioBeeper-PM.



Normal ECG tracing telephoned with CardioBeeper.

The CardioBeeper system is simple to use. Your patient need not undress. Or be bothered with paste, gels or straps. He simply places a reusable electrode in each bare armpit. And to transmit, he merely holds the CardioBeeper



monitor next to the mouthpiece of the phone while touching a button. *Physician and patient stay in constant voice contact while sending and receiving.*

You can immediately receive the telephoned data as a series of audible "beeps" indicating each QRS complex or pacemaker spike. To receive a permanent record of ECG or pacemaker artifact, just connect a CardioBeeper® ECG Decoder to your telephone and to any conventional ECG machine. Or instead, connect a CardioBeeper® Decodalyzer to your phone to obtain a visual readout of heart rate or pacemaker rate in BPM, interval count in msec. or a direct ECG tracing for your records.

In life-threatening emergencies or routine checks, no remote cardiac monitoring instruments available today at any cost can rival the revolutionary CardioBeeper system. For further information, simply contact your Wyeth representative or Wyeth Laboratories, Box 8299, Philadelphia, Pa. 19101.

Manufactured for Wyeth Laboratories by Survival Technology, Inc.

CardioBeeper®-PM
pacer monitor
CardioBeeper®
heart monitor

Wyeth Laboratories
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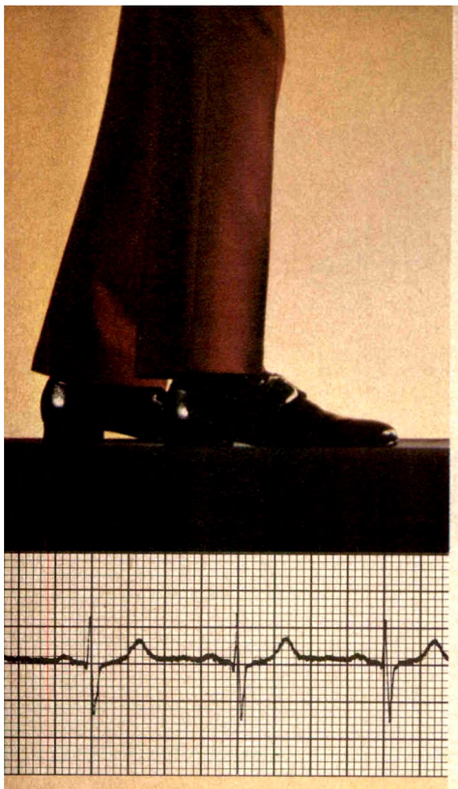
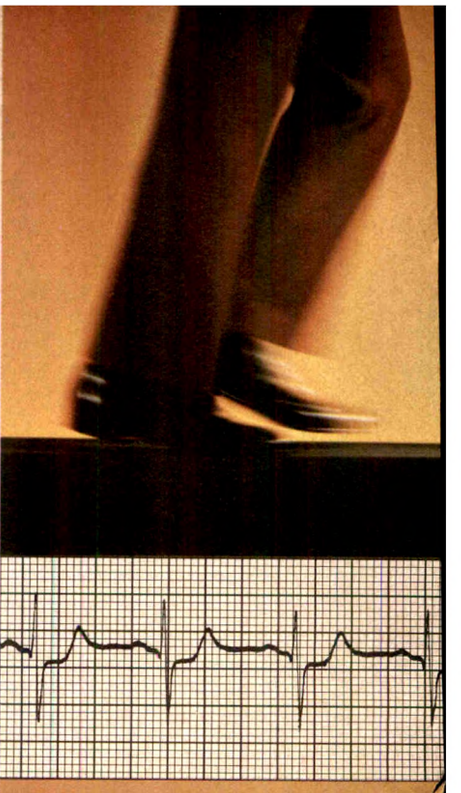


Standing, at rest, V-5, HR-74. American's Stress Test Electrode supplies immediate base line stability. Testing with a narrow, drift free base line can begin as soon as the self-adhering, silver/silver chloride electrodes have been applied to the patient and connections made to your monitoring equipment.

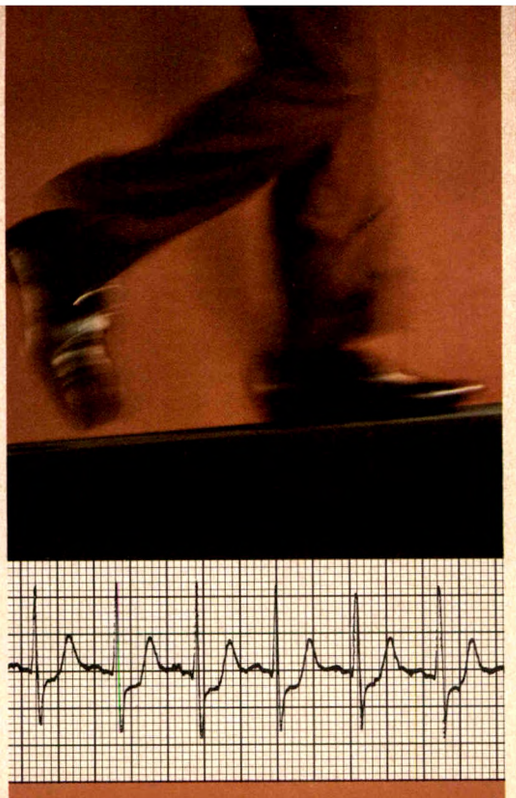
4th Minute at 2 mph, 0% Grade, V-5, HR-75. Base line stability is maintained because of the electrode's gel retaining cup and gel impregnated foam pad; the gel pad is slightly oversize to assure positive, continuous pressure at the electrode-skin interface. The result: virtual elimination of base line instability and motion artifact.



4th Minute at 3 mph (8th minute of test), 0% Grade, V-5, HR-83. (The patient's ECG indicates 1 mm of S-T depression.) Fully shielded cable and leadwire provide an effective barrier to the electrical interference that might otherwise mask small amounts of S-T depression.

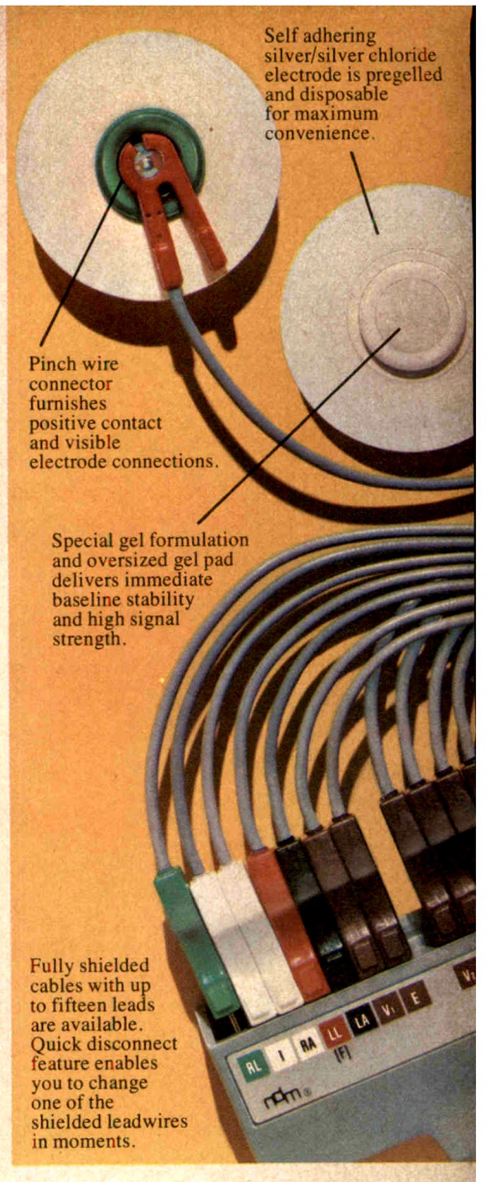
Do your stress test ECGs show everything you need to see?

n Minute at 3 mph (12th minute test), 5% Grade, V-5, HR-117. -T depression increases to 2.5 mm.) en at high work loads, the Ameri- n Stress Test Electrode and fully ielded cable system delivers a stable se line and noise-free signal.



4th Minute at 3 mph (16th minute of test), 7.5% Grade, V-5, HR-135. (S-T depression drops to 2.0 mm.) Long test procedures seldom affect the electrode's contact with a patient's skin; trace quality remains high, even with patients who perspire heavily.

(Because of this electrode's special gel formulation, application periods of longer than four hours are not recommended.)



Compare the stress test electrocardiograms you have been getting with those reproduced above.* There's a reason for the unusually high quality of the ECG traces shown: The patient was being monitored with American's Stress Test Electrode and fully shielded cable system.

If you've been diagnosing from stress test electrocardiograms that display wide or unstable base lines, severe motion artifact or possible hidden S-T depression, please contact us. We think we can help.

*Examples shown were produced under clinical conditions during an actual stress test procedure using the American Stress Test Electrode system.

We invite you to try the first electrode/leadwire/cable system designed to match the "no-compromise" nature of exercise stress testing. The fully shielded patient cable is adaptable to your present monitoring equipment, regardless of its make.

Please contact your American Hospital Supply or NDM representative to arrange a no obligation clinical trial, including a total inservice for your staff. American will supply electrodes, fully shielded cables and fully shielded, quick disconnect leadwires adaptable to your present monitoring equipment during the trial period.

For more information and a complimentary copy of our stress test technician's primer *How to Take the Strain out of Stress Testing,* write to: NDM, Department J, 3040 East River Road, Dayton, Ohio 45439.

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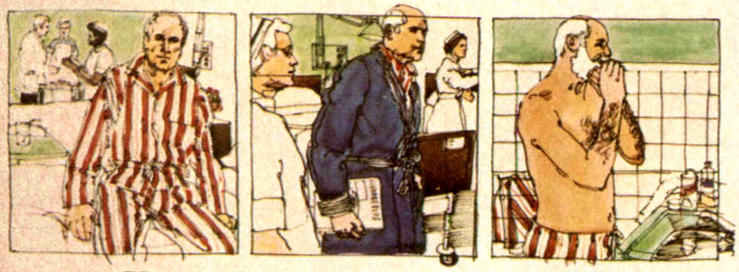
The Stress Test Electrode is protected by NDM Corporation by the following U.S. Patents: 3,696,807; 3,701,346; 3,713,435; 3,820,531

If psychic tension interferes with cardiac rehabilitation, here's how Valium® can help.
(diazepam)



During hospitalization, Valium (diazepam) can relieve psychic tension that can disrupt bed rest and interfere with the rehabilitation program.

After the MI patient is stabilized, a certain amount of psychic tension is to be expected. Your reassurance, counseling and enlistment of family support can often minimize its effects. However, in some instances, the patient's thoughts may dwell constantly on his condition and how it will affect his life, thus producing excessive psychic tension that may present special problems. He may feel overwhelmed and be so burdened by these tensions that he is unable to rest and unable or unwilling to begin a program of rehabilitation. Under these circumstances, Valium® (diazepam) can often be a beneficial adjunct.

Valium can calm the cardiac patient and help reduce his psychic tension to appropriate levels. Valium is used with most classes of primary medications such as cardiac glycosides, diuretics, vasodilators, anticoagulants, anticholinergics and antacids. Careful consideration should be given to the pharmacology of agents used with Valium, particularly those which may potentiate its action.

During convalescence at home, Valium (diazepam) can reduce excessive anxiety that may hinder participation in active rehabilitation.

Your counseling and the family's support do much to control the anxieties that may interfere with this stage of convalescence—a time when you may wish to encourage a gradual increase in activity. But in some patients, excessive anxiety may retard general progress. For them, Valium can be beneficial during the post-hospital transition to full ambulation. And, because the convalescent cardiac patient may be particularly prone to excessive tension and anxiety at bedtime, the addition of an *h.s.* dose of Valium to the *b.i.d.* or *t.i.d.* schedule can reduce these symptoms and thus may encourage sleep. Therapy with Valium should be discontinued when symptoms have been reduced to tolerable levels.

What an informed cardiac patient should know about Valium therapy.

The cardiac patient should know that he can generally expect Valium to help relax and calm him so that he won't feel so overwhelmed by his tension and anxiety. An explanation of the importance of the dosage regimen you prescribe may go a long way to ensure his cooperation. As with all CNS-acting agents, the patient taking Valium should be cautioned against driving or operating dangerous machinery.

Valium® (diazepam)

2-mg, 5-mg, 10-mg tablets can relieve the cardiac patient's undue psychic tension

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For a summary of product information, see the following page.

Valium® (diazepam)
2-mg, 5-mg, 10-mg tablets

can relieve the cardiac patient's undue psychic tension

Prompt and Effective Response Valium acts promptly to help relieve psychic tension in the cardiac patient.

Wide Margin of Safety At recommended dosages, oral Valium is generally well tolerated and does not significantly affect respiration, pulse or heart rate.

Flexible Dosage Available as *scored* tablets, oral Valium allows dosage to be easily readjusted to suit patients' changing needs.

Predictable Pharmacokinetically Pharmacokinetic studies of Valium demonstrate a highly predictable pattern of absorption, distribution, metabolism and excretion.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

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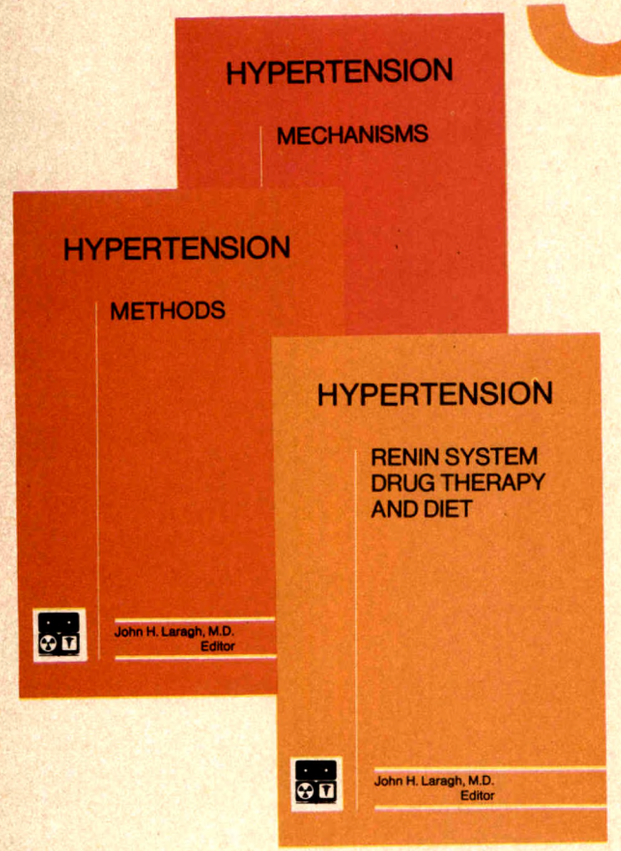

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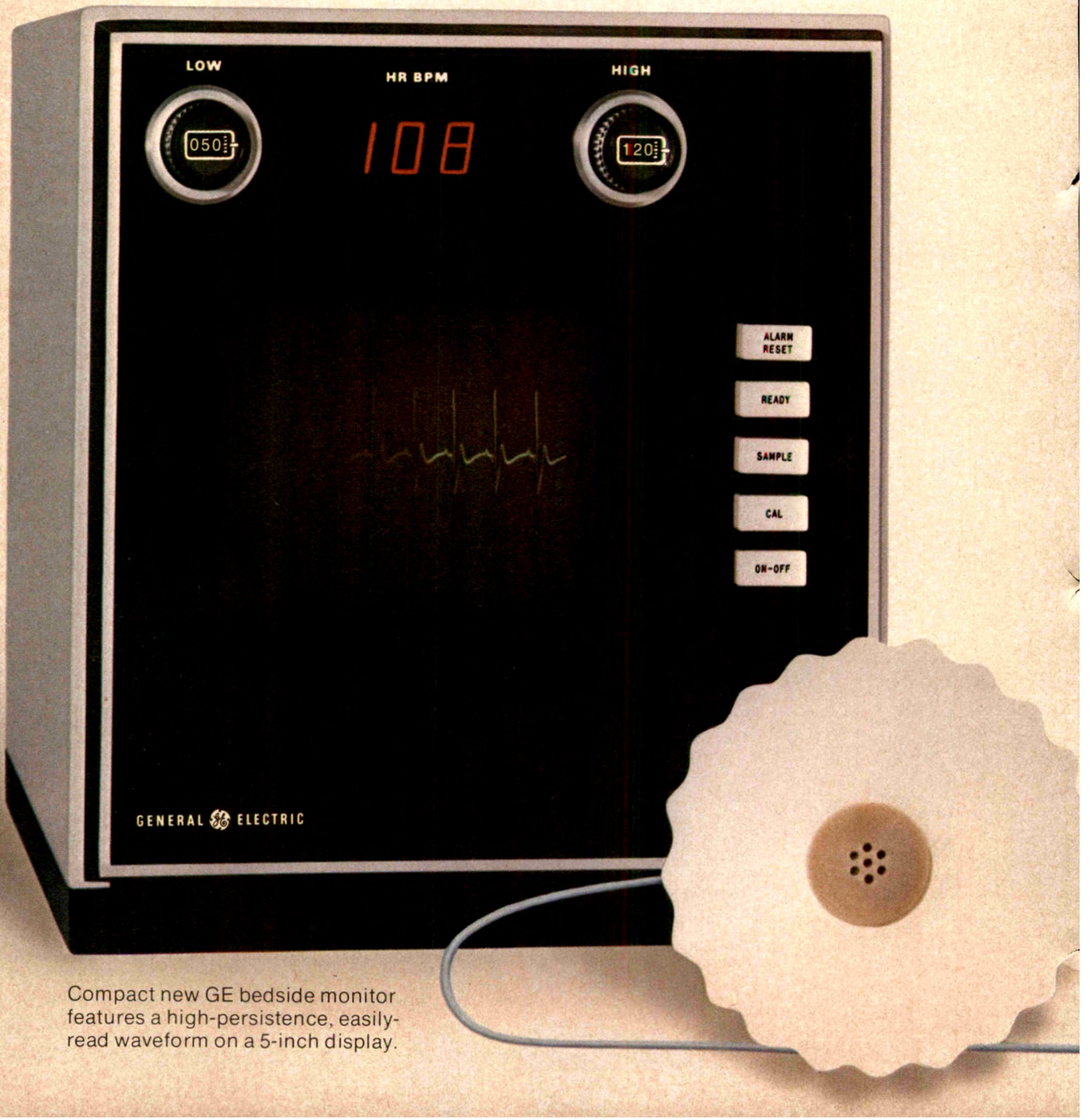

Compact new GE bedside monitor features a high-persistence, easily-read waveform on a 5-inch display.

1. Less signal drift.

Accurate patient monitoring begins with signal capture, and only General Electric offers Daisy™ electrodes, recognized by the industry for long-term monitoring effectiveness. Silver-silver chloride sensing element minimizes offset potentials and drift.

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GE's sophisticated signal recognition circuitry and artifact rejection separate the signal from the noise, presenting meaningful ECG complexes and digitally displayed data necessary for patient management.

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Because GE compensates for T waves, noise, and shifts in signal level, you're not plagued by false alarms. Should a lead fail, you're told just that, so you know it's not a patient problem.

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Automatic gain control adjusts to the R waves as they decrease or increase in size, thus accurate heart rates are provided without constant adjustment.

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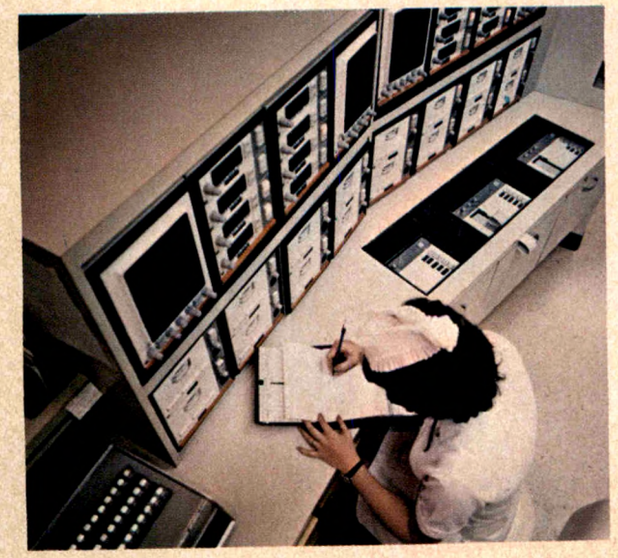

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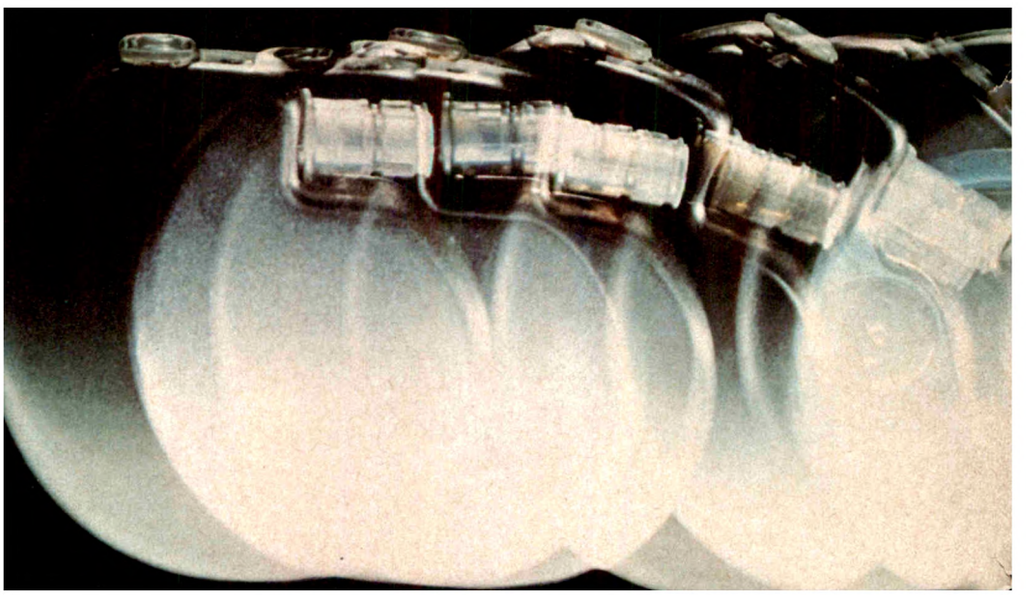

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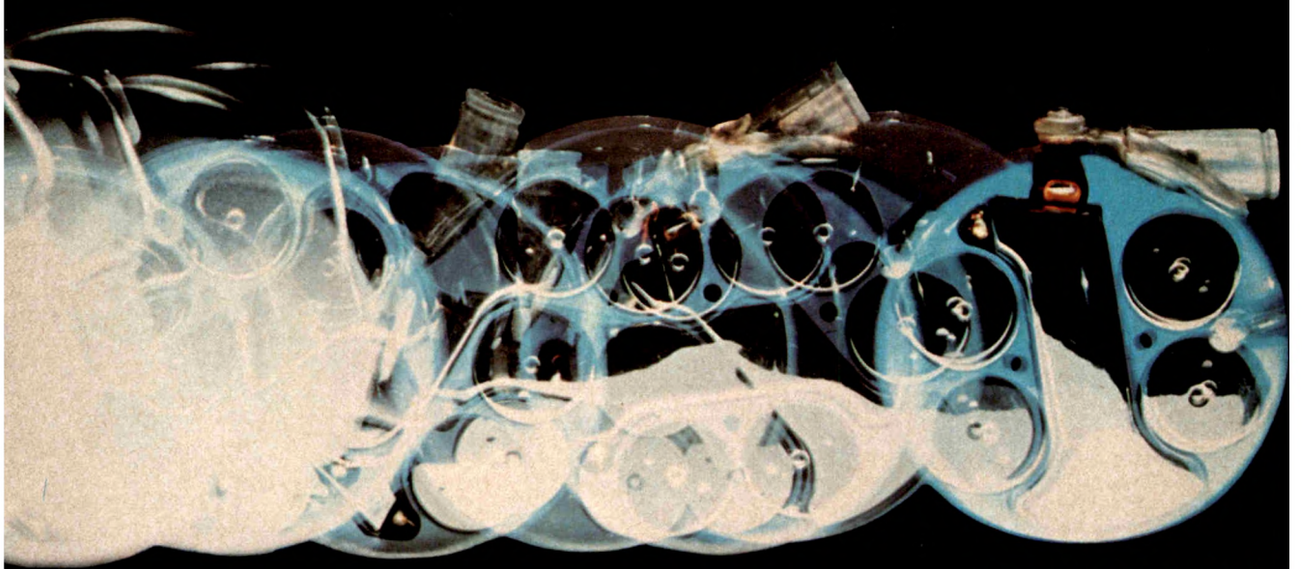

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Peritrate® SA Sustained Action
(pentaerythritol tetranitrate) 80mg

CAUTION: Federal law prohibits dispensing without prescription.

Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later. Tablets should not be chewed.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also in unit dose—package of 10 x 10 strips (N 0047-0004-11).

Additional Dosage Forms: Peritrate 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also in unit dose—package of 10 x 10 strips (N 0047-0001-11). Peritrate 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

Full information is available on request.

Defense against attack.

For over 22 years, Peritrate® has been considered by many physicians as one of the top defensive measures for patients with angina pectoris. In many patients Peritrate used prophylactically helps decrease the frequency and severity of angina attacks.* With minimal side effects.

Peritrate can also help reduce nitroglycerin requirements and, therefore, nitroglycerin side effects. Is it any wonder so many physicians continue to prefer Peritrate prophylaxis for their angina patients?

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The Great Wall of China, an immense 1,400-mile-long man made barrier 20 to 30 feet high and 15 to 20 feet thick, helped defend China from the attack of Mongol hordes for more than 2,000 years.

*The drug has been evaluated as possibly effective for this indication.
See brief summary.

With the introduction of the new Sterile Disposable Domes, Bentley Trantec offers safety, convenience and economy, previously unavailable. This has been accomplished by designing an isolating polycarbonate membrane into the dome itself. *Only* this membrane touches the transducer sensing surface, isolating the fluid in the dome from the non-sterile surface. It does not affect the sensitivity or fidelity of the transducer and the possibility of cross-contamination is completely eliminated.

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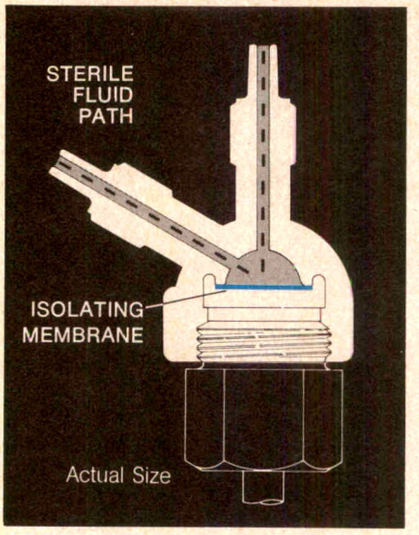

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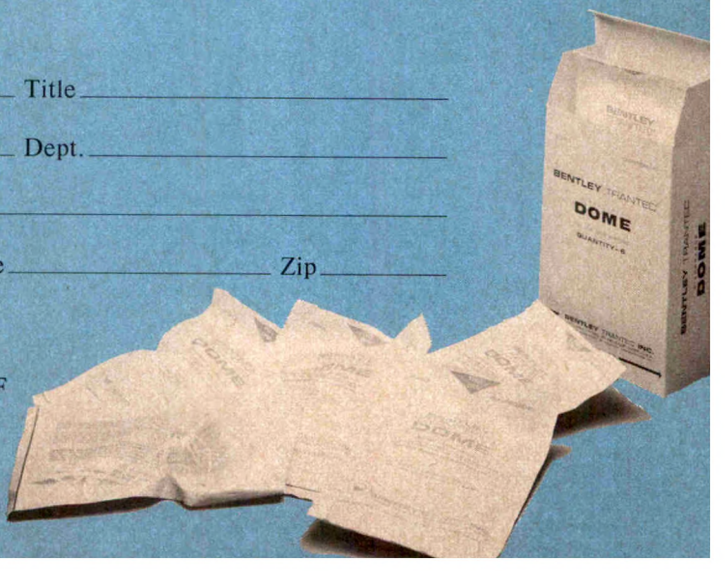

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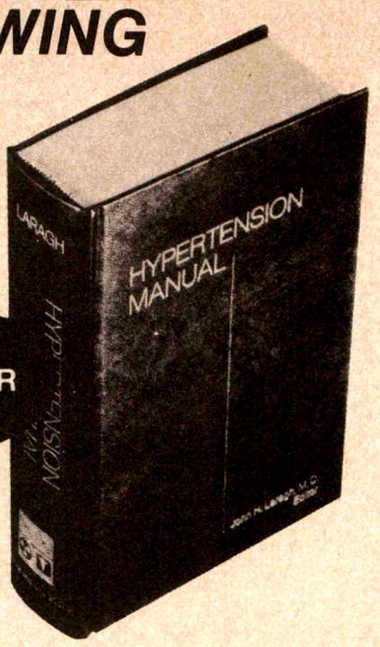

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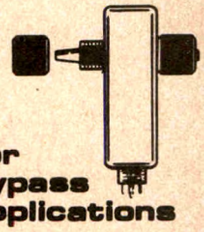

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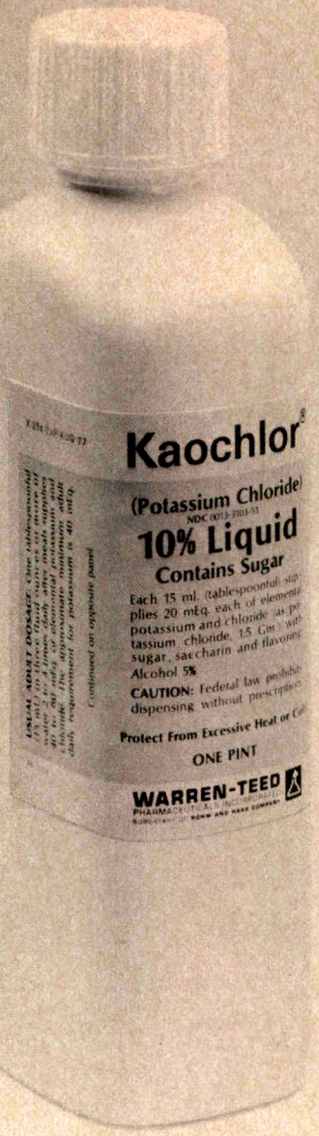

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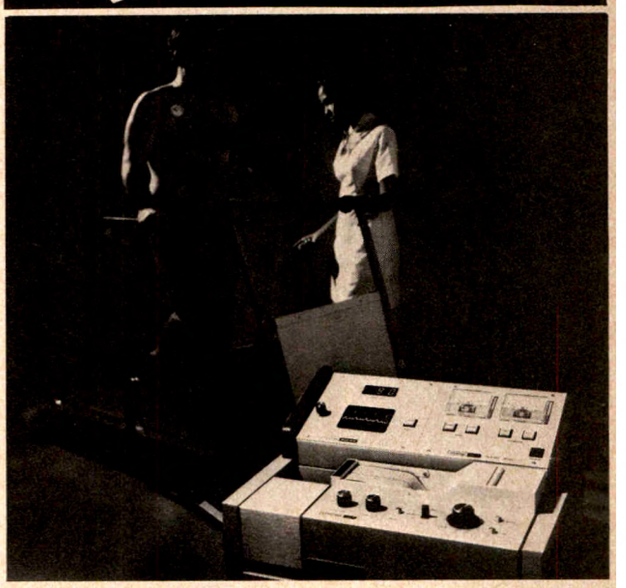

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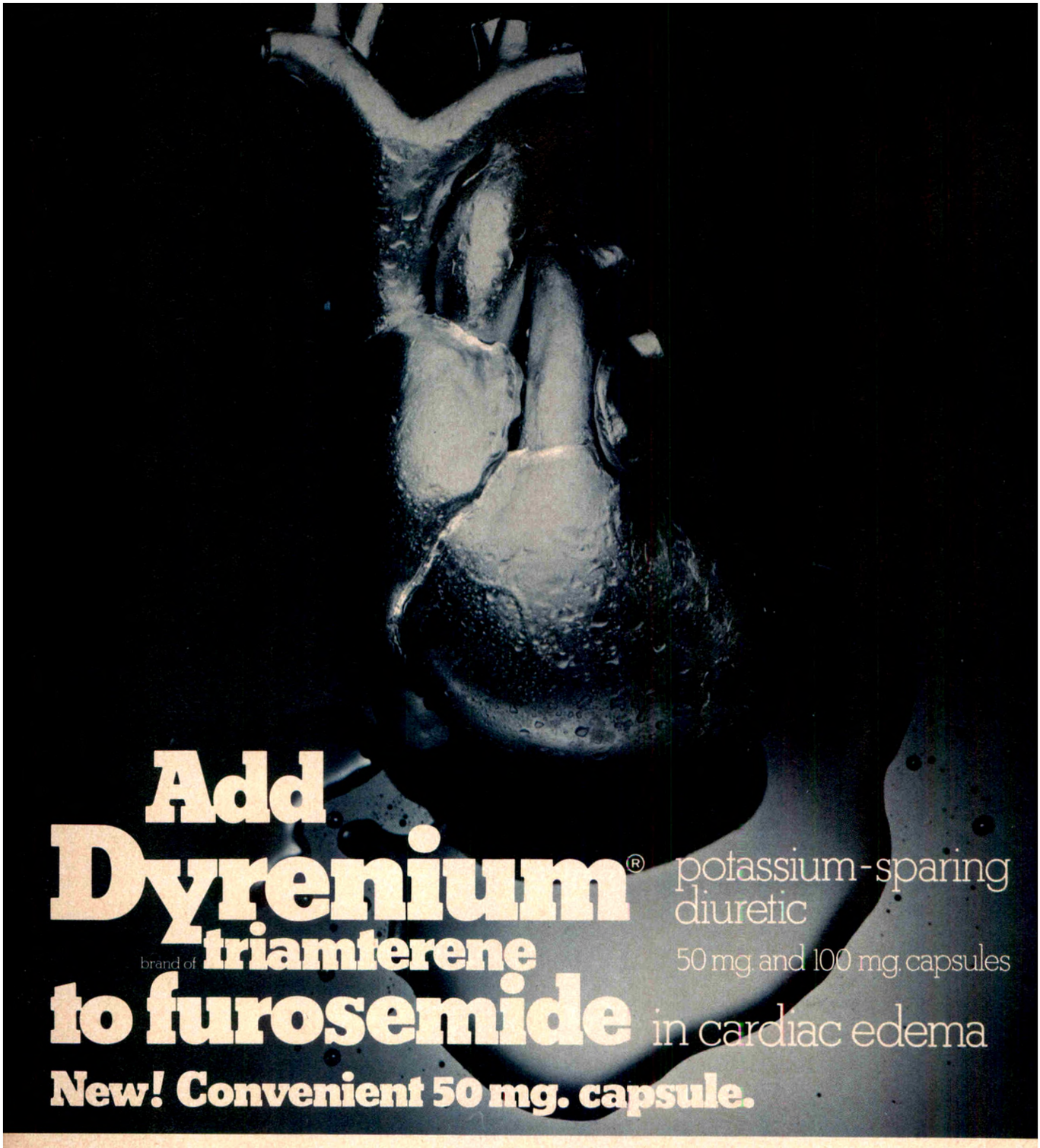

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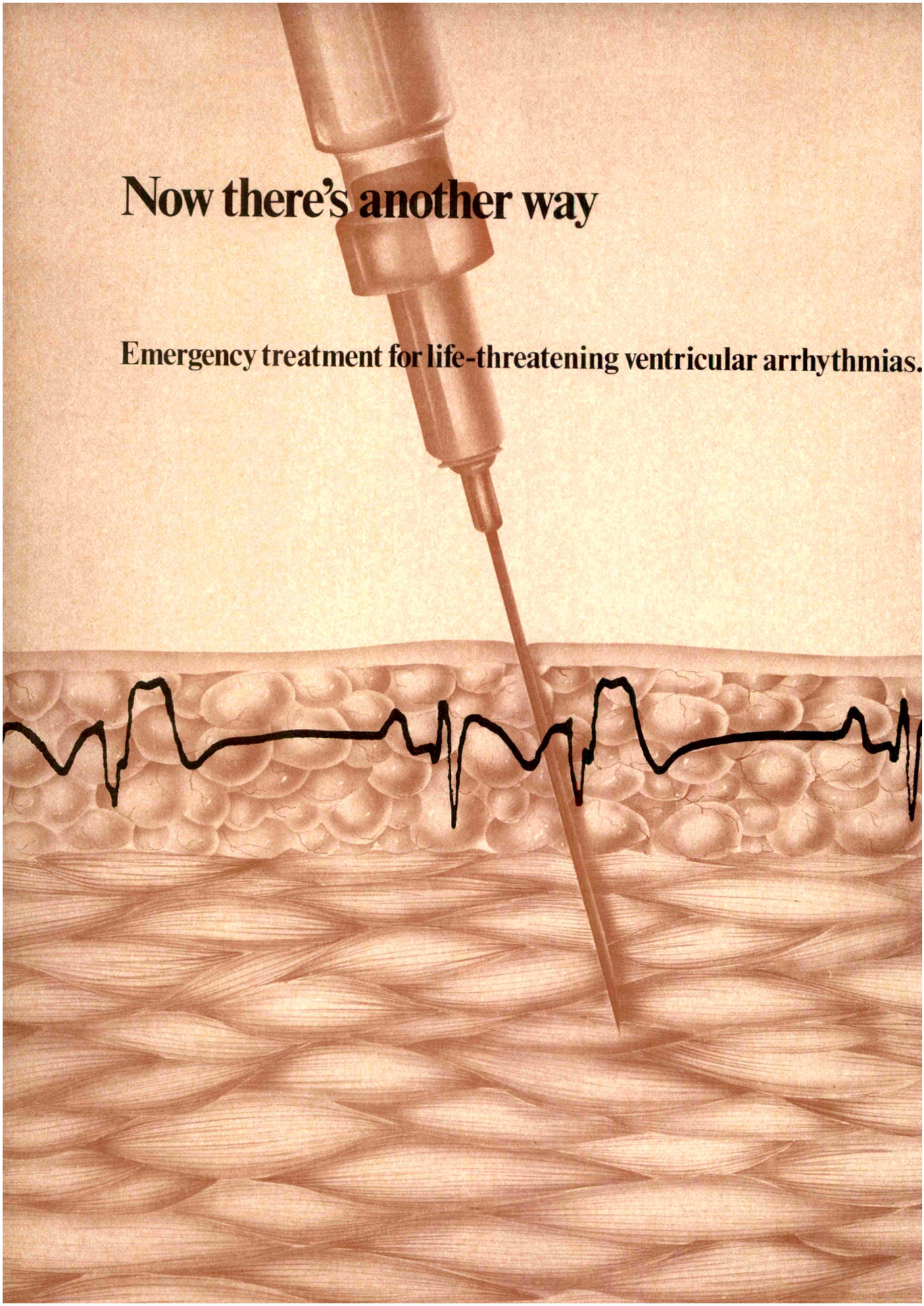
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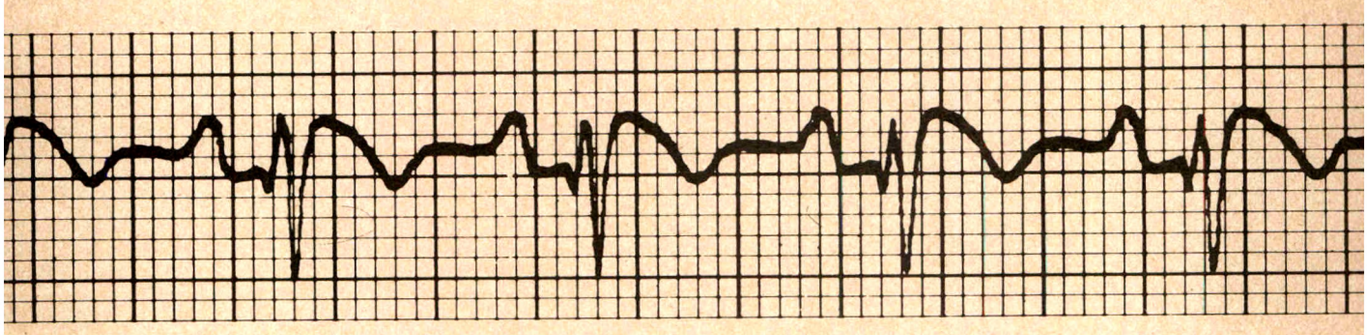

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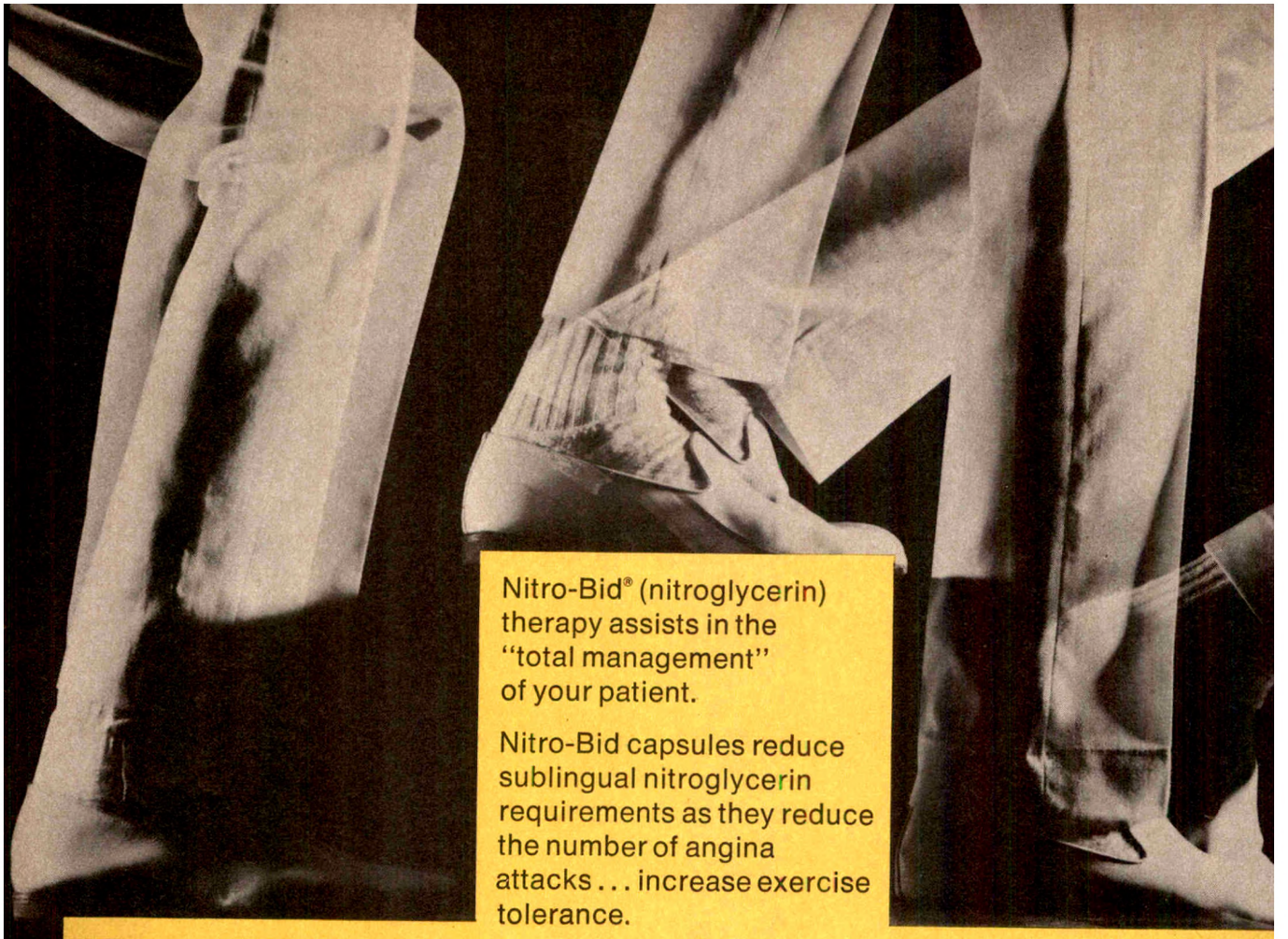

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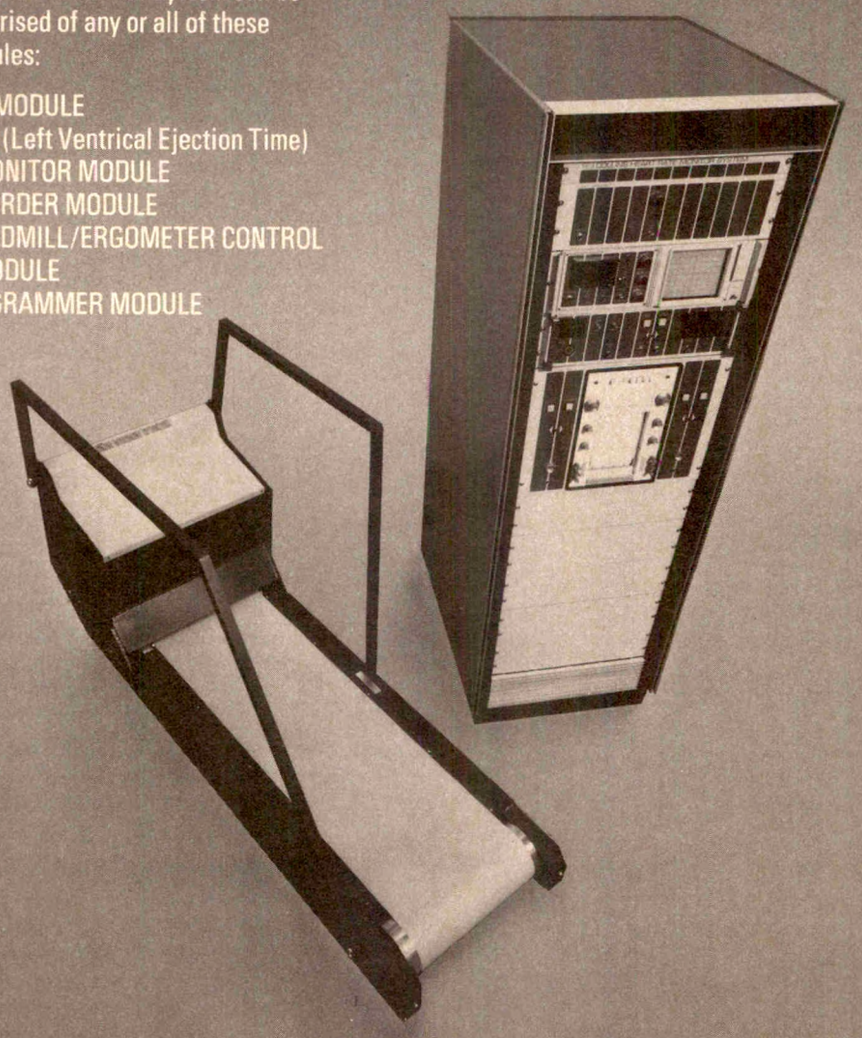

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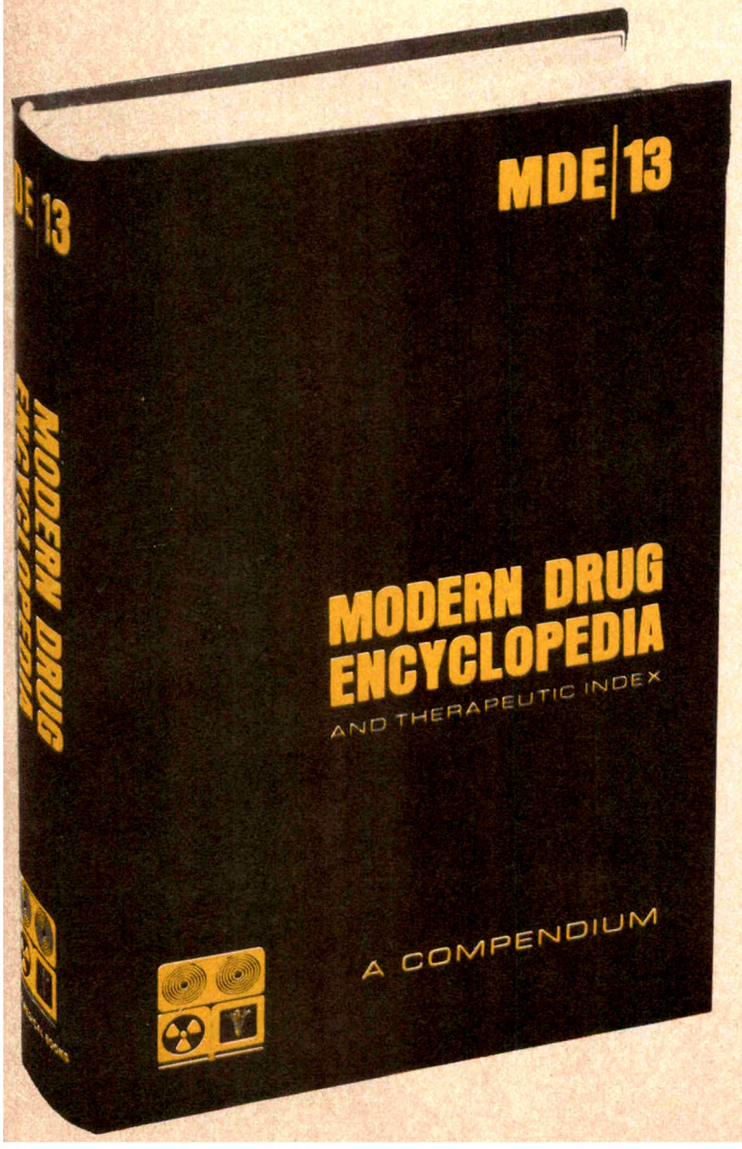

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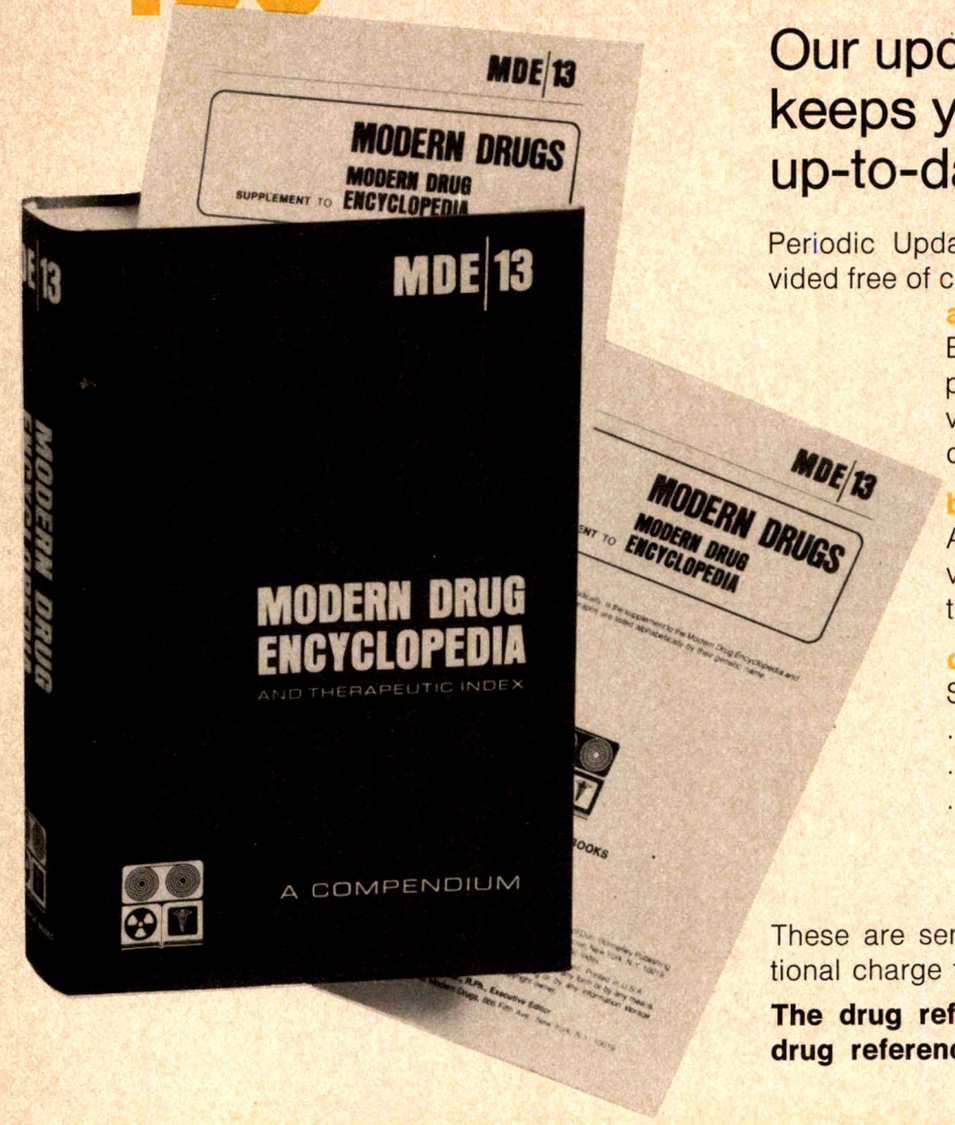

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Smaller, lighter compact one-piece unit weighs 25 ounces.

The Remler patented Ambulatory Blood Pressure Recorder has been in use for more than ten years by leading physicians and research institutions throughout the world.

Now, by miniaturizing circuits and components, we have produced a smaller and easier to wear single-unit version that weighs only 25 ounces.

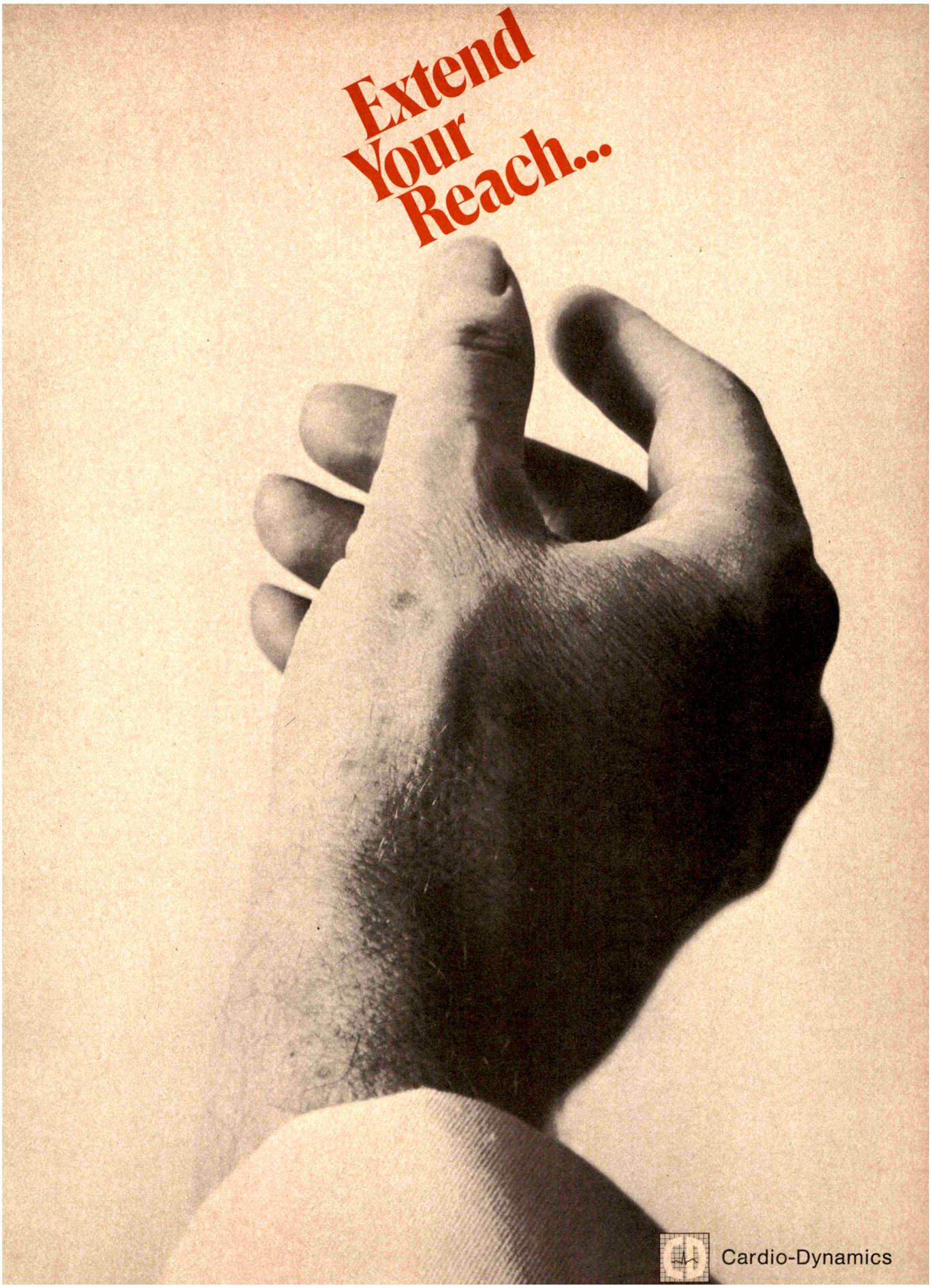
This new Model M-2000 records blood pressures during the wearer's working or leisure day. Wearing this unobtrusive, lightweight device on a belt, any patient can easily record blood pressure data onto the micro-cassette as many as fifty times daily. This method eliminates the pressor effect of an observer's presence.

The compact recording unit plugs into the physician's corresponding decoder for quick direct decoding on a permanent paper transcript which can be evaluated by the physician for indications of varying systolic and diastolic pressures and heart rate. The decoder's headphones aid in interpretation of Korotkoff sounds in the area of diastolic pressures.

The Remler system is especially useful in determining the efficacy of medication in the treatment of hypertension.

Please return the coupon for complete information.

Remler Company

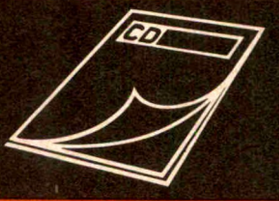

Extend
Your
Reach...
Cardio-Dynamics

The Dyna-Gram® Way

of Holter Electrocardiography extends the reach of your practice by providing you with sophisticated equipment, an expert staff and a complete ECG report that frees you to devote your time to diagnosis and treatment . . .

Equipment that is reliable and provides uninterrupted ambulatory, office-quality ECGs for up to 24 hours.

A team of professionals behind you devoted exclusively to the processing of Holter recordings with attention to accuracy and detail that is rarely equalled in office or hospital.



The recording is summarized in a report that provides a complete, standardized and documented digest of your patient's ECG.

All of this is the promise of Holter recording.

Cardio-Dynamics delivers the promise!

Cardio-Dynamics Laboratories Inc.
9454 Wilshire Boulevard
Beverly Hills, California 90212

Sales Agents:

SEARLE **Searle Laboratories**
Division of G. D. Searle & Co., Chicago, Illinois 60680

Year after year, cardiologists throughout the world specify the Ekoline 20® more often than all other ultrasonoscopes combined.

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To achieve and maintain such clear-cut leadership, SKI provides superior instrumentation and unsurpassed product support, including a clinically trained sales staff, a top technical staff, and worldwide service centers.

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Number One for ten straight years.

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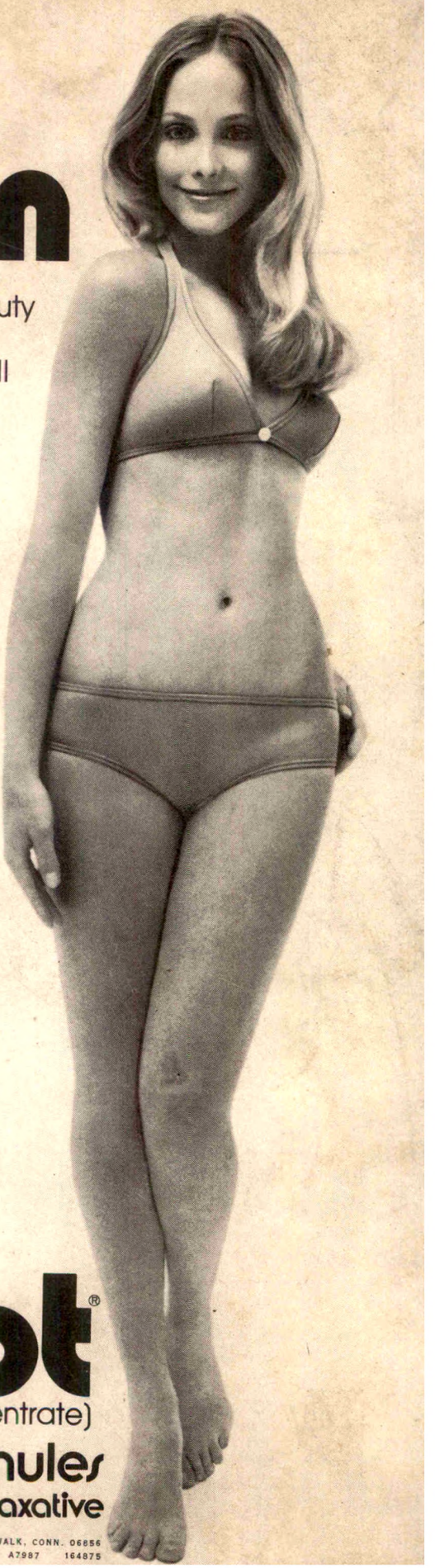

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Standardized senna concentrate has two claims to natural distinction. In SENOKOT Tablets/Granules, it is standardized for uniform action. And it is prepared from the deseeded pod of Cassia acutifolia, discarding the leaves that contain coarse resins.

Virtually colon-specific, SENOKOT Tablets/Granules provide gentle, predictable overnight laxation...usually without side effects at recommended dosage levels. As regular elimination is established, dosage can be reduced gradually and eventually discontinued.

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a natural vegetable laxative

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SEPTEMBER 1975

The American Journal of CARDIOLOGY®

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Review of Tricuspid Atresia

Symposium on Reperfusion During Acute Myocardial Infarction—Part II
Eliot Corday, MD, FACC and Samuel Meerbaum, PhD, FACC, Guest Editors

Call for Abstracts: ACC 25th Annual Scientific Session
New Orleans, Louisiana, February 23-26, 1976

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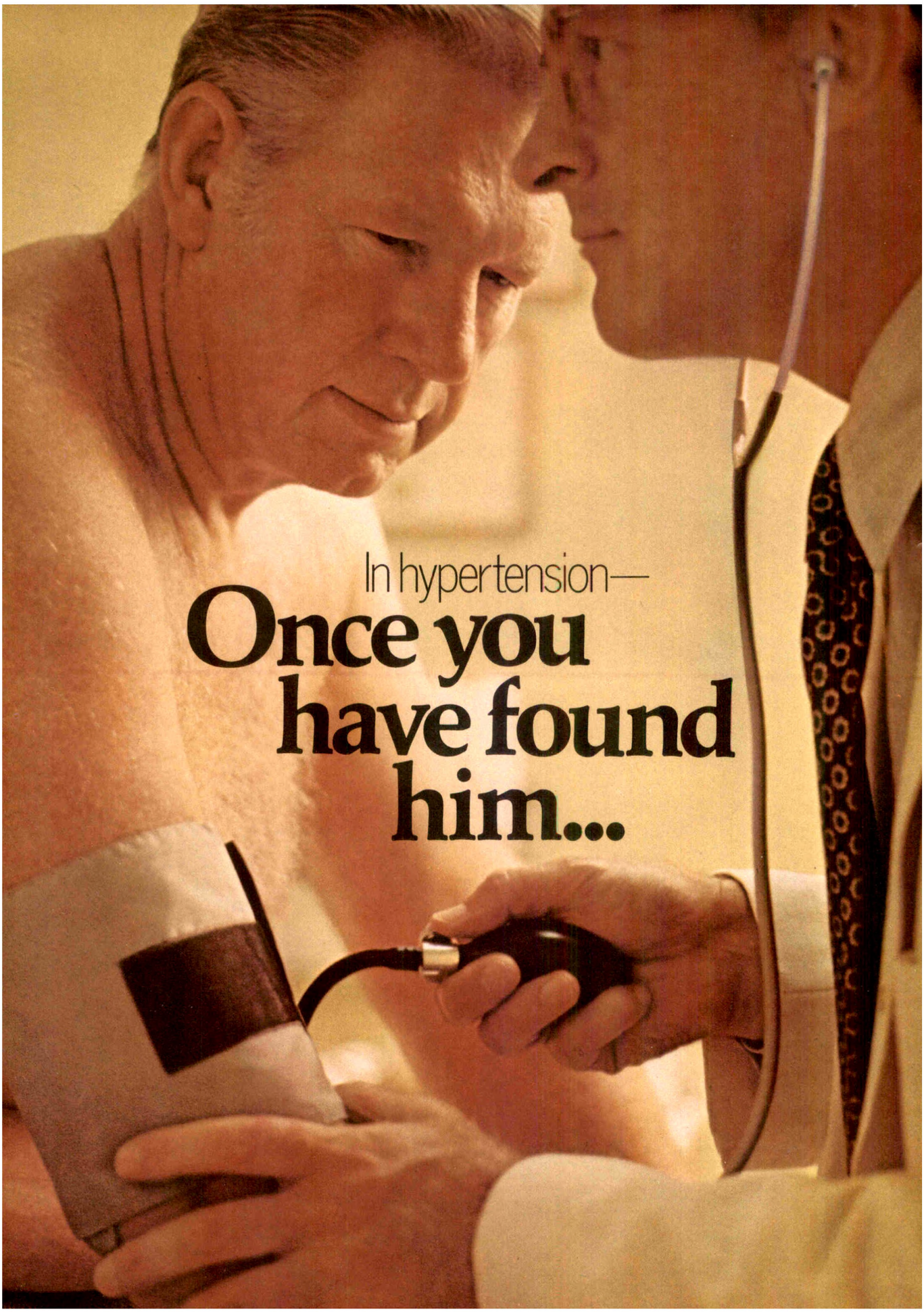
In hypertension—
Once you have found him...

TABLETS, 25 mg and 50 mg

HydroDIURIL®

(HYDROCHLOROTHIAZIDE | MSD)

a basic therapeutic approach to hypertension

The importance of early diagnosis in hypertension, so that appropriate treatment can be initiated promptly, has been well established.

Authorities in cardiovascular medicine have come more and more to favor the thiazides as initial drug therapy in early essential hypertension—for several important reasons.

initial medication that is often effective when used alone

The thiazides are well-established baseline therapy. Their effectiveness in lowering blood pressure has been thoroughly documented, and this effectiveness fits the needs of most patients with mild hypertension. Many hypertensives can be maintained for years on thiazide therapy.

suitable when used with other agents

Equally important is the usefulness of the thiazides in combination with other antihypertensive agents, when they are indicated. This retention of the thiazide in the regimen provides a useful baseline upon which the physician may build a therapeutic program. Since thiazides may add to or potentiate the action of other antihypertensive drugs, careful observation for changes in blood pressure must be made.

HydroDIURIL
(HYDROCHLOROTHIAZIDE, MSD)
often an excellent choice

HydroDIURIL is highly effective antihypertensive therapy, initially and over the long term—the results it has helped achieve over many years with many patients make it especially worth your consideration in the early treatment of hypertension.

Contraindications include anuria and hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs. Use with caution in patients with severe renal disease, impaired hepatic function, or progressive liver disease.

For a brief summary of prescribing information,

MSD
MERCK SHARP &

Once you have found him...

HydroDIURIL®

(HYDROCHLOROTHIAZIDE | MSD)

in the management of hypertension

Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs; routine use in an otherwise healthy pregnant woman with or without mild edema.

Warnings: Use with caution in severe renal disease since thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Use in pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy or in women of childbearing potential, weigh anticipated benefit against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.

Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 25 mg hydrochlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 50 mg hydrochlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Tablets containing 100 mg hydrochlorothiazide each in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

addendum

MSD
MERCK SHARP & DOHME

"Required Reading" For Your Hypertensive Patients

Because of the importance of patient motivation, Merck Sharp & Dohme offers "High Blood Pressure," a concise, pocket-sized booklet that defines the patient's own role in the management of hypertension. This booklet is available for you to give to your patients. It is designed to reinforce your explanation of hypertension and it emphasizes the importance of patient understanding in adhering to the regimen you prescribe.

Please ask your Merck Sharp & Dohme Professional Representative or write Professional Service Department, West Point, Pa. 19486 for a supply of this booklet.

IN ANGINA*: ACTS WITH SUBLINGUAL SPEED

CHEWABLE SORBITRATE® 5MG.
ISOSORBIDE DINITRATE

As with sublingual ISDN:
acts in 2 minutes for therapeutic use...
acts up to 2 hours for prophylaxis.

In addition:
chewing action helps distribute nitrate over a larger mucosal area.

SUMMARY OF
PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.
Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.
Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.
Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.
Dosage and Administration: Route: Sublingual, oral and chewable tablets.
Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.
Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:
Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.
Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.
It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS
Division of ICI United States Inc.
Wilmington, Delaware 19897

to help increase blood supply in treatable vasospastic disorders*

Brief Summary

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).

USV PHARMACEUTICAL MFG. CORP.
Manati, P.R. 00701

USV PHARMACEUTICALS

Arlidin® 6 mg.
(nylidrin HCl)

Dilates arterioles[1]...maintains mean arterial blood pressure[1]...postural hypotension not reported† Arlidin also offers dosage flexibility...is adjunctive to supportive therapy...and provides a favorable benefit-cost ratio, too.

†See Adverse Reactions section in Brief Summary.

1. Innes, I.R. and Nickerson, M.: Drugs acting on postganglionic adrenergic nerve endings and structures innervated by them (sympathomimetic drugs), in The Pharmacological Basis of Therapeutics (Goodman, L.S. and Gilman, A., eds.), ed. 4, New York, Macmillan,

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Long before
facing the
"ultimate" test
of stability...

Nitrostat has shown proof of stability

There are a lot of ways to say "stable" when you're dealing with nitroglycerin. Some more meaningful than others.

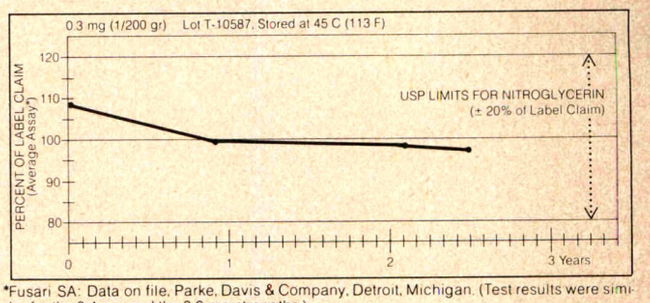
That's why the testing of Nitrostat *includes* tests to simulate, as closely as possible, the actual conditions of use.

For example, we test for **wickability** — a Parke-Davis test (the time in seconds required for water to wet the tablet completely by capillary action under controlled conditions) — to simulate under-the-tongue conditions.

Heat-stable? Yes. Up to 45 C (113 F) (considerably higher than your patient's pocket temperature). See graph.

What's more, the crucial question of maintenance of content uniformity of nitroglycerin is answered by Nitrostat as proved by assay.

Potency? The average assay still shows almost 100% of label claim more than 30 months after manufacture: less chance of your patient taking a superpotent or, more important, a subpotent tablet.



*Fusari SA: Data on file, Parke, Davis & Company, Detroit, Michigan. (Test results were similar for the 0.4-mg and the 0.6-mg strengths.)

Disintegration? We test it using the USP test in 800 ml of water — all tablets usually disintegrate within 30 seconds (USP limit — two minutes).

Dissolution? Using NF Method II, we show greater than 90% dissolution in 30 seconds.

Now, each factor taken by itself may not be decisive. But taken together, they add up to a good reason to specify Nitrostat.

Nitrostat® / sublingual tablets stabilized formula

(nitroglycerin tablets, USP)

0.3 mg (1/200 gr)
0.4 mg (1/150 gr)
0.6 mg (1/100 gr)

...the tested and proved one

Please have representative deliver a supply of the following. (Check block)

☐ Patient booklets:
"What you should know about angina."

☐ Patient starter packages of Nitrostat.®
(nitroglycerin tablets, USP)

PHYSICIAN'S NAME

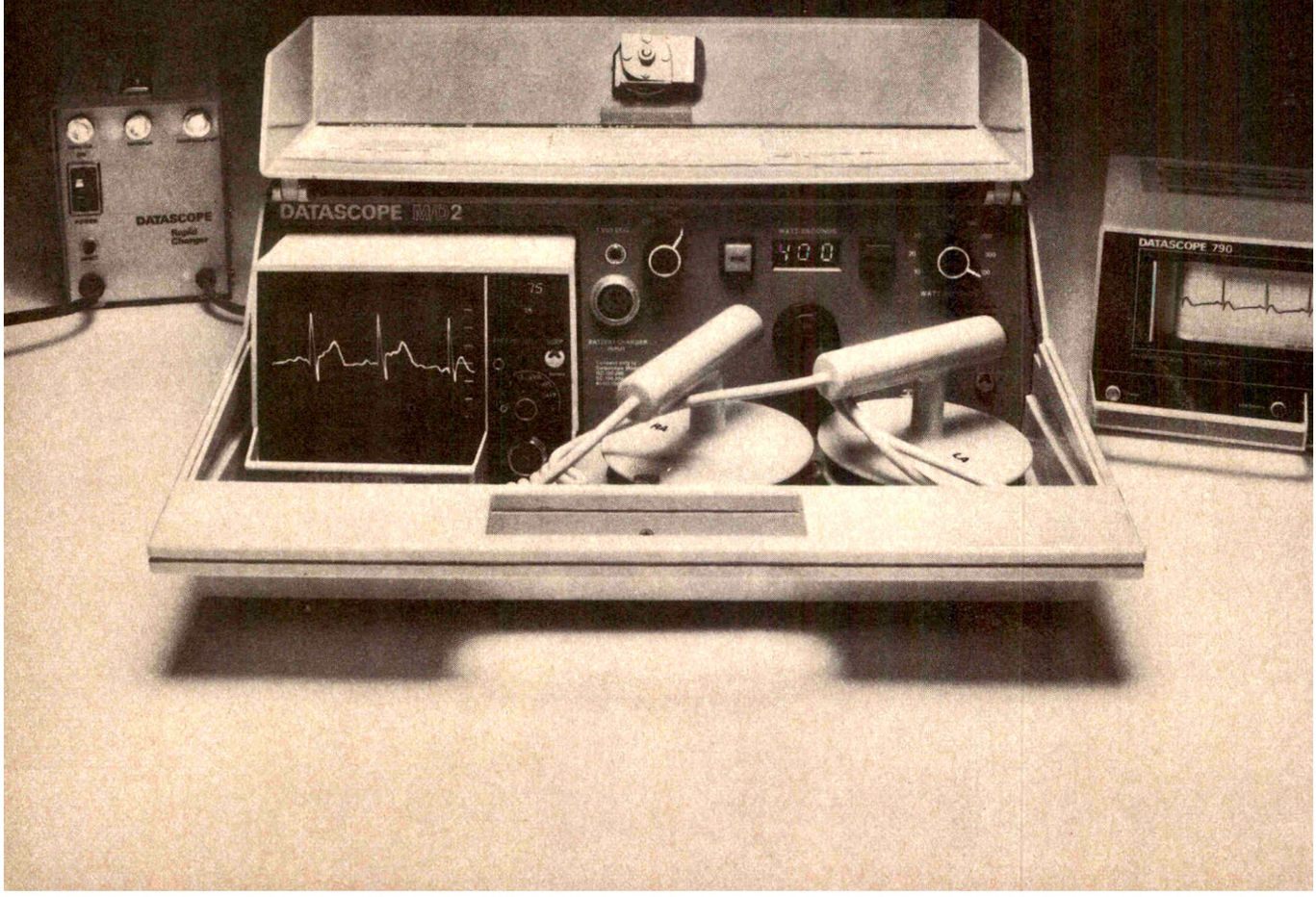
ADDRESS

Available in bottles of 100 and new Convenience Packs of 25

PARKE-DAVIS

Parke, Davis & Company

THE DATASCOPE M/D2 SYSTEM THE FIRST RESCUE SYSTEM AS FLEXIBLE AS THE PEOPLE WHO USE IT.



If there's one thing you can
sure of in cardiac rescue, it's
at you can't be sure of anything.

Every situation, either in the
spital or in the field, presents
w problems, and requires new
lutions.

At Datascope, we've been in
nergency medicine since its
ception.

Our equipment has faced just
out everything. And from that
perience we've put together a
stem that's prepared to face
ything: the M/D2 System.

The M/D2 System is built on
e very simple principle. *Every
strument in the system must be
dependent and not compro-
ised by any other instrument.*

In keeping with this philoso-
y, our monitor, our defibrillator
d our strip-chart recorder each
ve a separate battery source.
ne unit never puts a drain on
other.

But to see its flexibility, let's
ke our system apart, instrument
/ instrument.

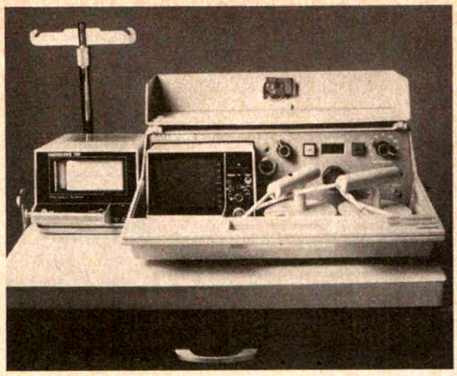
OUR MONITOR.

The monitor in the M/D2
stem nests inside the defibril-
tor. You can carry the monitor
d defibrillator, use it, and store
as one unit.

But the monitor pulls out* of
e M/D2 case and works as a
parate unit as well. So it can be
aced right on a patient's stretcher
the field. Or put in the most
lvantageous viewing position at
e bedside.

In addition to being so flex-
ible, our monitor outperforms any
monitor in emergency medicine.

It has a 5-inch scope with a
8 x 11 cm. viewing area.



It has a memory which pro-
vides a bright, non-fade display
that's remarkably clear even in
strong sunlight.

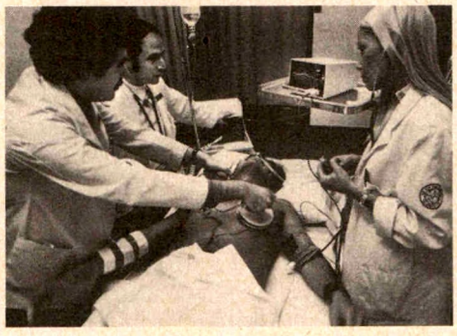
It has a freeze button which
lets you stop the ECG for closer
study.

It's the only emergency moni-
tor with a digital heart rate read-
out. And because the readout is
an LED display, you can even read
it in the dark.

OUR DEFIBRILLATOR.

Like our monitor, our defib-
rillator has its own battery-pack.

It's the only defibrillator made
that gives you a *digital* energy
meter. Which displays both stored
energy and the results of delivered
energy tests.



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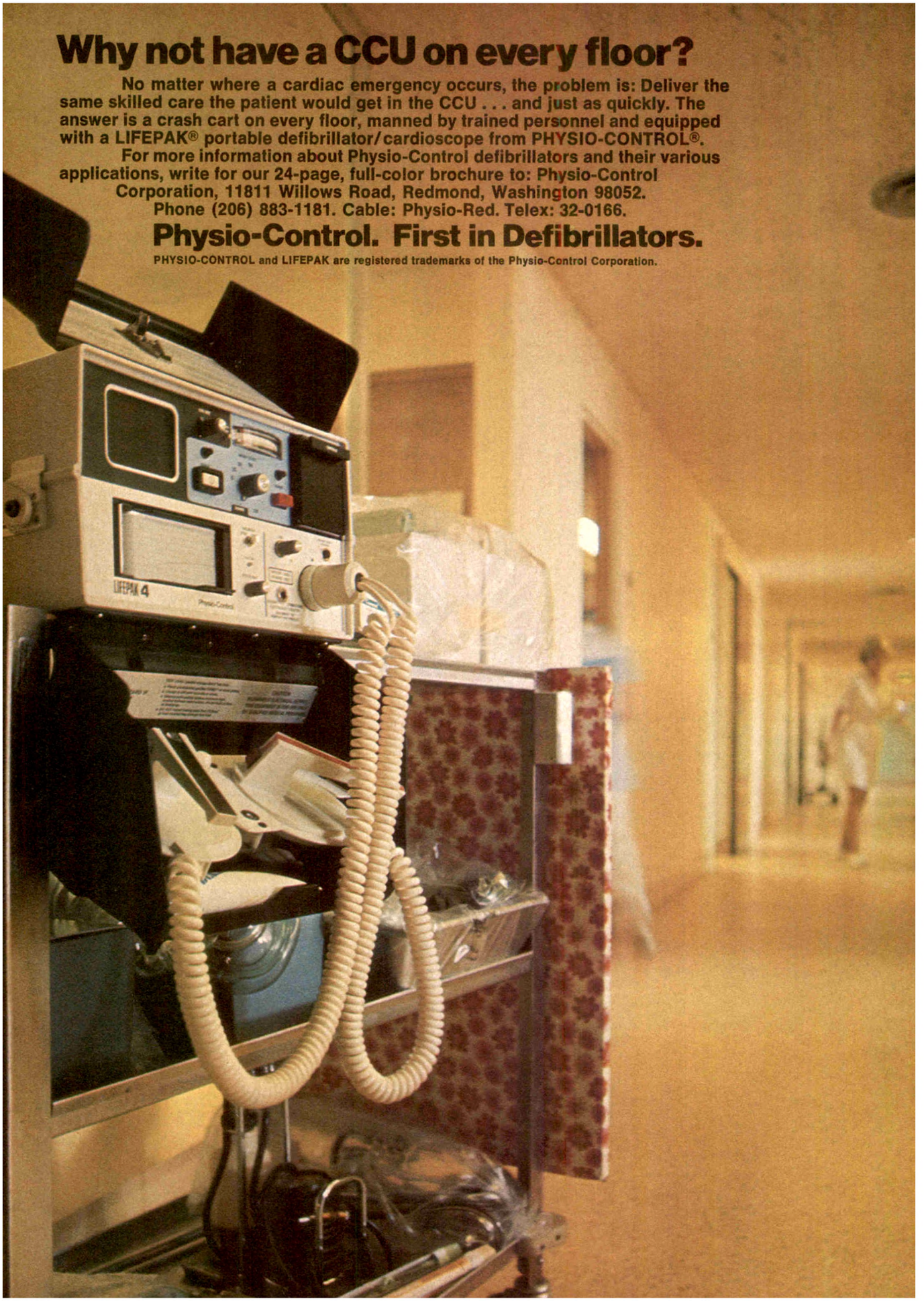

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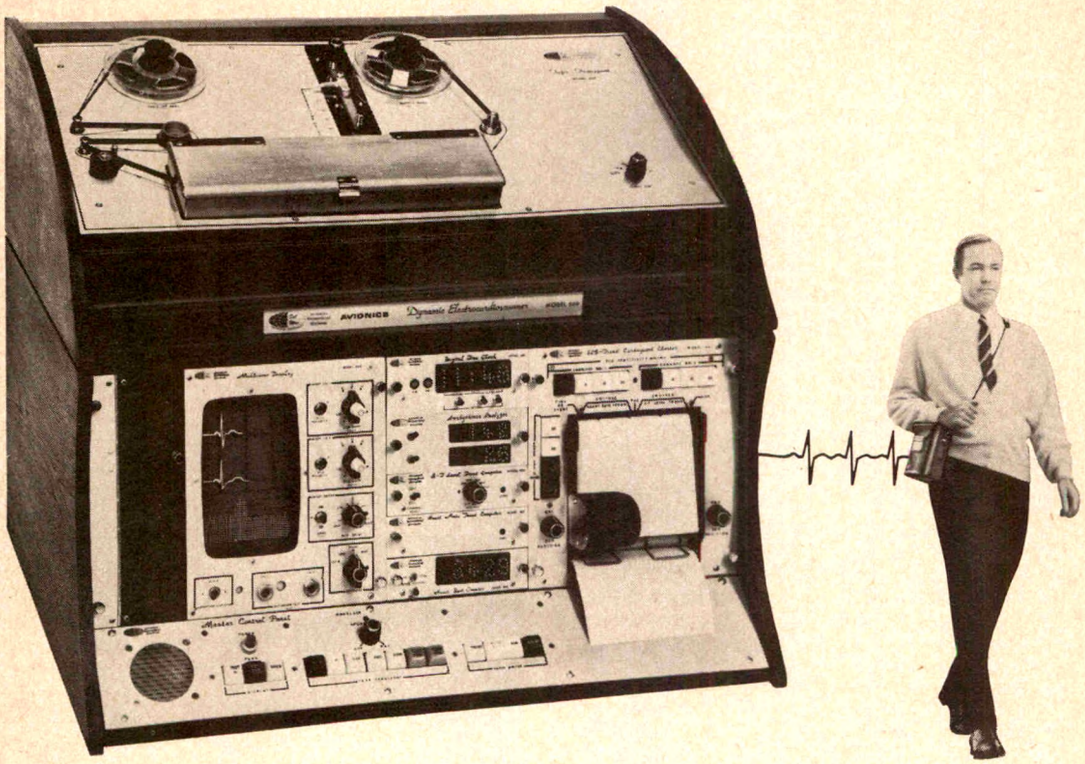

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281 **New Observations on the Effects of Atropine on the Sinoatrial and Atrioventricular Nodes in Man**

GOPAL DAS, FREDERICK N. TALMERS and ARNOLD M. WEISSLER

In normal volunteers the response of the sinoatrial (S-A) node to various doses (0.1 to 0.8 mg) of atropine was bimodal, slowing at smaller doses and accelerating at larger doses. The atrioventricular node showed accelerated conduction at all dosage levels. These observations suggest caution in the use of atropine in patients with acute myocardial infarction. Smaller doses may paradoxically aggravate bradycardia and larger doses may precipitate tachyarrhythmias.

286 **Induction of Atrioventricular Nodal Reentrant Tachycardia After Atropine. Report of Five Cases**

MASOOD AKHTAR, ANTHONY N. DAMATO, WILLIAM P. BATSFORD, ANTONIO R. CARACTA, JEREMY N. RUSKIN, GERALD M. WEISFOGEL and SUN H. LAU

The intravenous administration of 0.5 mg of atropine provided the necessary balance of conduction and refractoriness within the atrioventricular (A-V) nodal reentrant pathways to produce and sustain A-V nodal reentry in five patients with no history of supraventricular tachycardia. This effect may help to explain the success of digitalis and propranolol in the management of supraventricular tachycardia, since these agents prolong refractoriness of the A-V node and abolish A-V nodal reentry.

292 **Quantitative Study of the Supernormal Phase of Ventricular Excitability in Man**

MASAO IGARASHI and TAKAO AYABE

Ten of 11 patients with acute and chronic bradyarrhythmias studied by fixed rate endocardial pacing manifested a supernormal phase of excitability either early or late in diastole. Its duration depended on the intensity of subthreshold stimuli. Ventricular excitability was not uniform throughout diastole and could be enhanced unexpectedly late in diastole by summation of impulses. This could be the basis for the Wedensky facilitation phenomenon.

297 **Hereditary Progressive Atrioventricular Conduction Defect**

HENRY T. LYNCH, SYED MOHIUDDIN, JANE MORAN, ARNOLD KAPLAN, MICHAEL SKETCH, ALAN ZENCKA and VINCENT RUNCO

Concordance analysis of the hereditary progressive atrioventricular conduction defect in the affected parents and offspring of Family S (a kindred of 1,067 members) suggests a Mendelian autosomal dominant factor is responsible for transmission of the diathesis for the defect. The empiric risks for heart block in offspring of affected parents range from 0.16 to 0.31 and in siblings from 0.01 to 0.50. The pathogenesis of the syndrome is unknown.

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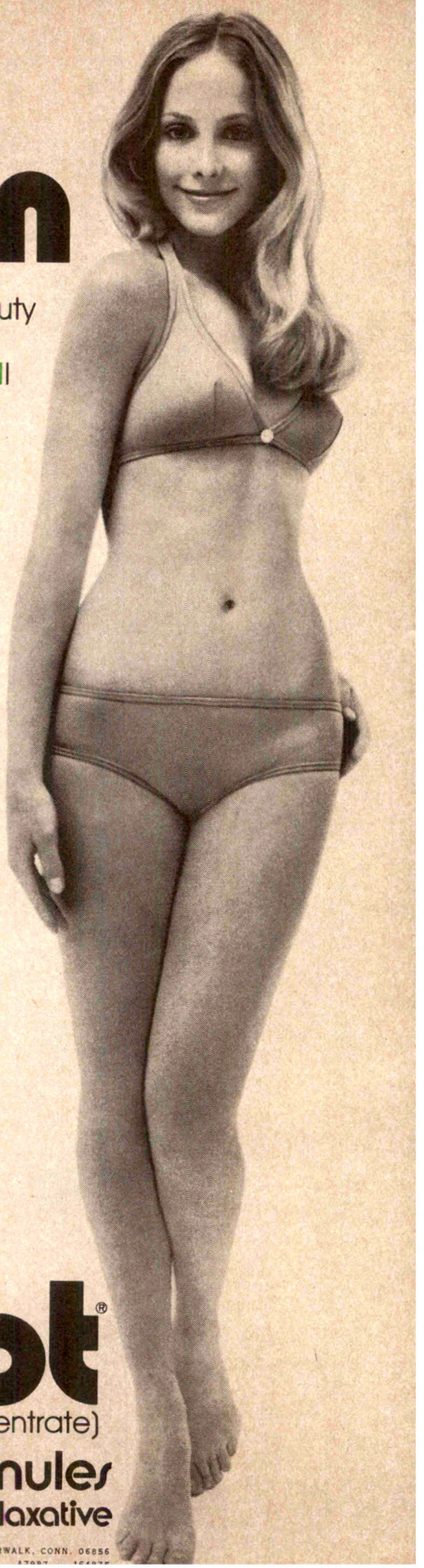

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KENNETH A. POPIO, RICHARD GORLIN, LOUIS E. TEICHHOLZ, PETER F. COHN, DAVID BECHTEL and MICHAEL V. HERMAN

The left ventricle in 12 adults with an ostium secundum atrial septal defect was subnormal in volume, abnormal in sequence of contraction of the septum (early systolic bulging toward right ventricle), and characterized by apparent decreased distensibility. These findings suggest that the superimposition of a mild degree of stress, such as hypertension, age, atrial fibrillation or mitral regurgitation, may precipitate clinical heart failure.

309 **Phasic Left Ventricular Blood Velocity Alternans in Man**

KENNETH B. DESSER and ALBERTO BENCHIMOL

Direct measurement of the blood cell velocity in the left ventricle of conscious man by Doppler catheter velocimetry relates alternans of phasic left ventricular blood velocity to an altered inotropic state during cardiac acceleration or to beat to beat variations in end-diastolic fiber length. Critical right atrial or ventricular pacing rates required to produce blood velocity alternation ranged from 100 to 160 beats/min.

315 **The Coronary Arteries in Marfan's Syndrome. A Morphologic Study**

ANTON E. BECKER and JAN-PAUL van MANTGEM

In four of the five hearts in these cases of Marfan's syndrome studied microscopically, the extramural coronary arteries showed accumulations of acid mucopolysaccharides and concomitant disruption of the connective tissue elements. The intramural coronary arteries were generally unaffected. The possibility of such coronary arterial involvement should be considered in all patients with Marfan's syndrome.

METHODS

322 **Clinical Applications of the Threshold Tracking Pacemaker**

THOMAS A. PRESTON and DAVID L. BOWERS

Limited clinical testing of the threshold tracking pacemaker indicates its potential effectiveness and safety in patients requiring temporary pacing for acute cardiac problems. This new generation fully automatic pacemaker searches for and finds the threshold level and adjusts its stimulus to just above this level. It ensures an adequate safety margin of stimulation but reduces the stimulus level to the lowest safe level possible.

PEDIATRIC CARDIOLOGY

327 **Tricuspid Atresia: Clinical Course in 101 Patients**

MACDONALD DICK, DONALD C. FYLER and ALEXANDER S. NADAS

Fifty percent of 101 patients with all forms of tricuspid atresia survived to 15 years of age. Although the overall surgical mortality rate was 23 percent, surgical intervention in those with decreased pulmonary vascularity improved the prognosis from a 10 percent chance to survive the first year of life to a 50 percent chance to survive to 15 years of life. Early surgical palliation appears to be promising.

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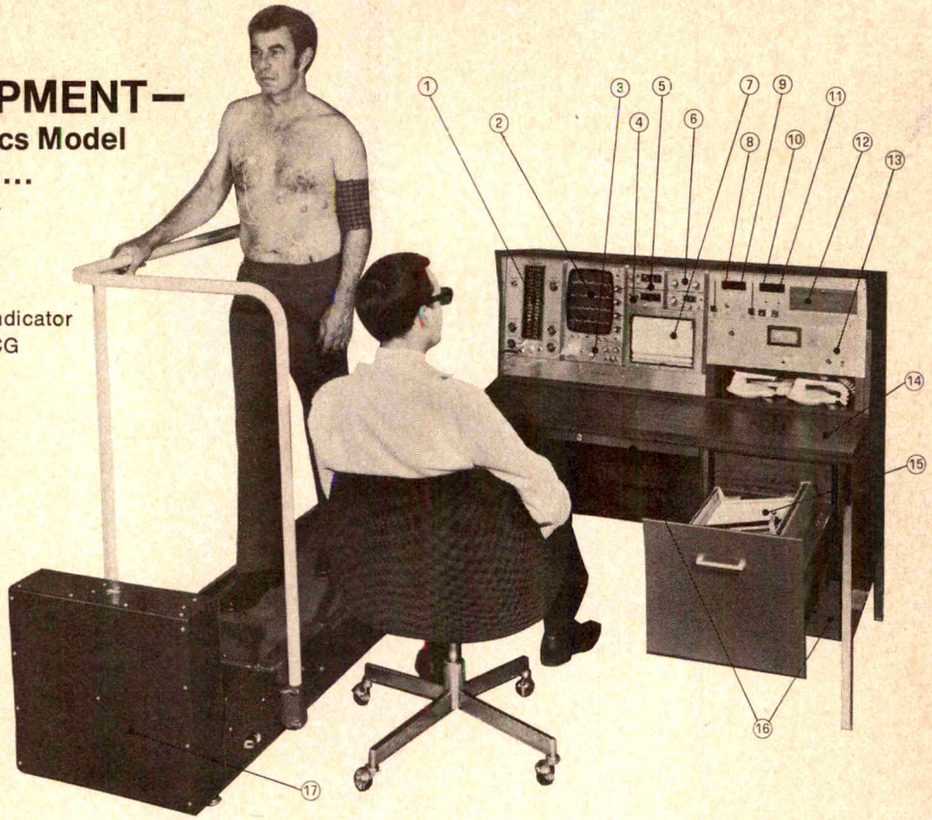

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338 Surgical Experience in Patients with Marfan's Syndrome, Ascending Aortic Aneurysm and Aortic Regurgitation

ANTOINE T. NASRALLAH, DENTON A. COOLEY, YOUSSEF GOUSSOUS, GRADY L. HALLMAN, ROBERTO LUFSCHANOWSKI and ROBERT D. LEACHMAN

The 5 year survival rate of 42.8 percent following surgical treatment of aortic insufficiency and ascending aortic aneurysm in 30 patients with Marfan's syndrome indicates that surgical treatment should not be withheld despite the underlying biochemical defect and potential future catastrophic complications in such subjects.

342 Coronary Artery Bypass in Patients Over 70 Years of Age: Indications and Results

JOSEPH MEYER, DON C. WUKASCH, WALTER SEYBOLD-EPTING, LUIGI CHIARIELLO, GEORGE J. REUL, Jr., FRANK M. SANDIFORD, GRADY L. HALLMAN and DENTON A. COOLEY

Improved surgical technique and postoperative care as detailed in this report are responsible for the reduced hospital mortality rate of only 4.8 percent in 21 patients operated upon during the first 6 months of 1974 compared with the overall mortality rate of 22.1 percent in all 95 patients over the age of 70 undergoing aortocoronary bypass. Such reduced mortality makes such operations in this age group less controversial.

DIAGNOSTIC SHELF

346 Echocardiographic Findings of Ventricular Septal Rupture in Acute Myocardial Infarction

ROBERT L. DeJOSEPH, STUART F. SEIDES, ANTON LINDNER and ANTHONY N. DAMATO

In an 80 year old man with a ventricular septal defect after acute myocardial infarction, the major echocardiographic change occurred in the upper portion of the septum. This area, showing only slight anterior motion during systole before the rupture, demonstrated, after rupture, a marked posterior motion with the onset of ventricular diastole, presumably representing passive motion of a flail dyskinetic septum.

349 Echocardiographic Findings in Uhl's Anomaly. Demonstration of Diastolic Pulmonary Valve Opening

JAMES W. FRENCH, DAVID BAUM and RICHARD POPP

Echocardiography helps differentiate Uhl's anomaly (congenital hypoplasia of the right ventricular myocardium) from Ebstein's disease of the tricuspid valve. Diastolic opening of the pulmonary valve was demonstrated by echocardiography in this 14 year old girl with Uhl's anomaly. Increased right ventricular dimension, delayed tricuspid valve closure and prolapse of the mitral valve were also observed.

354 Echocardiogram in Calcified Mitral Anulus

DAVID S. HIRSCHFELD and BIANKA B. EMILSON

These two case reports indicate that the echocardiogram of calcified mitral anulus mimics that of pericardial effusion but may be differentiated by demonstrating the abrupt termination of mitral ring echoes during sweep from the left ventricle to the left atrium. In contrast, there is a gradual diminution of the posterior or echo-free space in true pericardial effusion.

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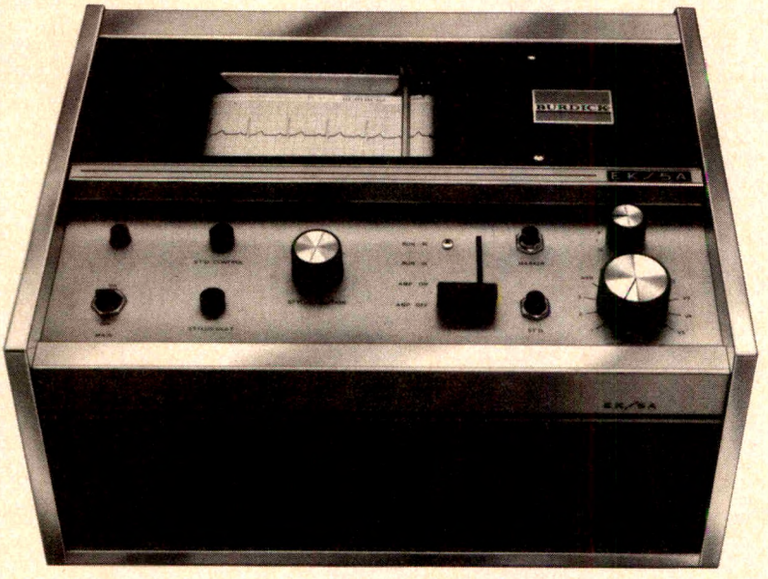

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CASE REPORTS

357 Reticulum-Cell Sarcoma with Intracardiac Metastases. Case with Angiocardiographic Improvement After Chemotherapy

CESAR A. CONDE, JOSE MELLER, JOHN PANTAZOPOULOS, EPHRAIM DONOSO and SIMON DACK

This is the first report of a case in which angiography demonstrated resolution of an intracardiac metastatic tumor after chemotherapy. This 66 year old man with reticulum-cell sarcoma eventually died from progressive multiorgan involvement.

363 Echocardiographic Diagnosis of Right Atrial Extension of Wilms' Tumor

ZIA Q. FAROOKI, JAMES G. HENRY and EDWARD W. GREEN

This report describes the fourth instance of direct propagation of a Wilms' tumor to the right atrium through the inferior vena cava and the first echocardiographic diagnosis of such extension in a child. This case differs from the others in that there was invasion of the surrounding structures and the tumor metastasized to the liver, rendering the condition inoperable.

SYMPOSIUM ON REPERFUSION DURING ACUTE MYOCARDIAL INFARCTION—PART II

368 Revascularization After 3 Hours of Coronary Arterial Occlusion: Effects on Regional Cardiac Metabolic Function and Infarct Size

COSTANTINO COSTANTINI, ELIOT CORDAY, TZU-WANG LANG, SAMUEL MEERBAUM, JOHN BRASCH, LEO KAPLAN, STEVEN RUBINS, HERBERT GOLD and JULES OSHER

In closed chest dogs two beneficial effects of revascularization after 3 hours of occlusion included significant reduction of average infarct size and restoration of cardiac function by the 7th day. Adverse effects included swelling of the ischemic myocardium and abnormal cardiac metabolic and mechanical function for at least 1 hour after reperfusion. This confirmed the unstable character of the early phase of reperfusion resulting in inadequate coronary reflow and metabolic derangements whereas prolonged reperfusion for 7 dogs reversed these adverse effects.

385 Consequences of Coronary Arterial Occlusion on Remote Myocardium: Effects of Occlusion and Reperfusion

ELIOT CORDAY, LEO KAPLAN, SAMUEL MEERBAUM, JOHN BRASCH, COSTANTINO COSTANTINI, TZU-WANG LANG, HERBERT GOLD, STEVEN RUBINS and JULES OSHER

Microinfarcts and regional lactate derangements were observed in the remote segments of the right and left ventricles of closed chest, normotensive dogs after acute occlusion of the proximal left anterior descending coronary artery. These changes, often irreversible, are attributed to ischemia of the remote myocardium that accompanies an acute coronary occlusion.

Continued on page A 21

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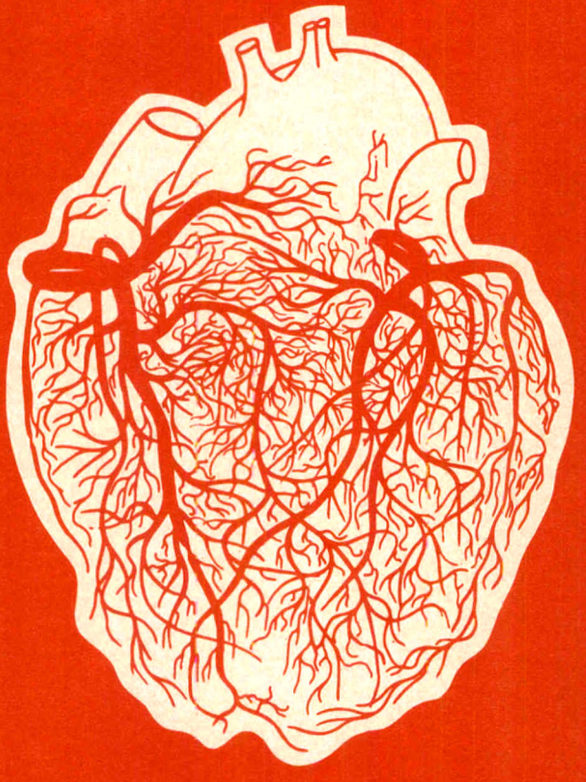

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Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.
Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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395 Myocardial Revascularization After Acute Infarction

HOOSHANG BOLOOKI *with the assistance of* MICHAEL D. KOTLER, LAWRENCE LOTTENBERG, STEPHEN DRESNICK, ROBERT C. ANDREWS, STEVEN KIPNIS and RICHARD M. ELLIS

Reperfusion of an area of myocardium ischemic for less than 2 hours in dogs or less than 4 hours in man may significantly reduce the extent of infarction and improve cardiac function as measured by cardiac catheterization and angiography. However, the revascularized area remains angiographically dyskinetic and electrocardiographically abnormal. This difference in time suggests a greater tolerance of the human myocardium to ischemia, most likely due to the presence of numerous intercoronary collateral communications and the insidious onset of coronary obstruction. This study emphasizes that the duration of ischemia before reestablishment of blood flow in an acutely occluded coronary artery in man must be limited to 4 hours.

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Predictive Value of Enzyme Studies in Myocardial Infarction—Galen et al.

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417 American College of Cardiology News

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CMS — Clinical Monitoring Systems — is an advanced, computerized monitoring system developed by B-D Electrodyne, a medical instrumentation division of Becton, Dickinson and Company.

It provides more meaningful information more quickly, and in a more easily assimilated form, than conventional or even other computerized systems.

For example:

Status. Composite, moment-to-moment status displays of each patient for each variable. Easily visible, even at a distance.

Rhythm history. 8 or 24 hour history of each patient. Large-screen graphic display.

Trend graphs of any monitored variable.

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Alphanumeric-labeled ECG strips. Each automatically labeled with time, date, bed number, patient name, status, beat classification.

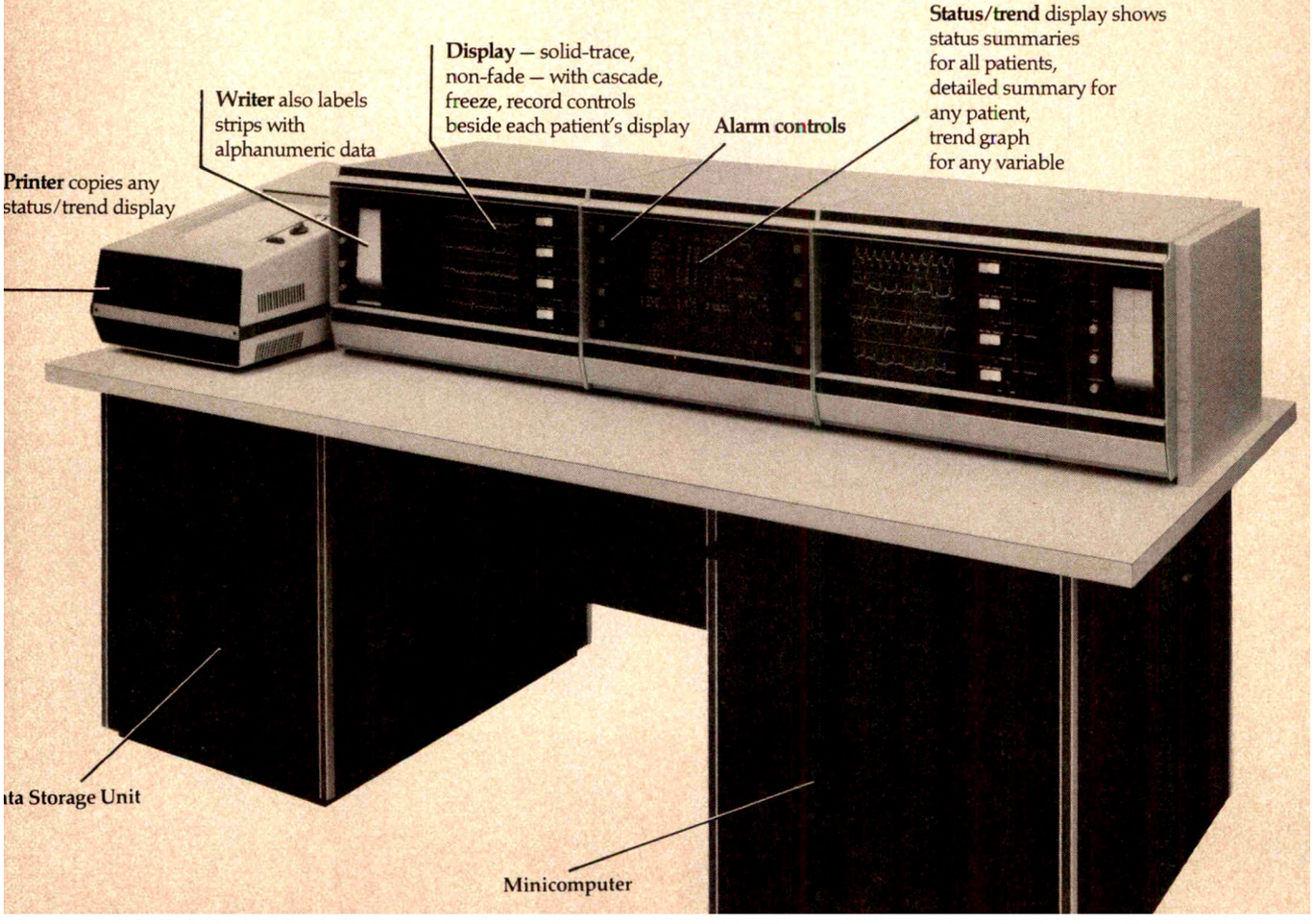
Hard copies of any display at any time.

Medication report. Type, amount, time.

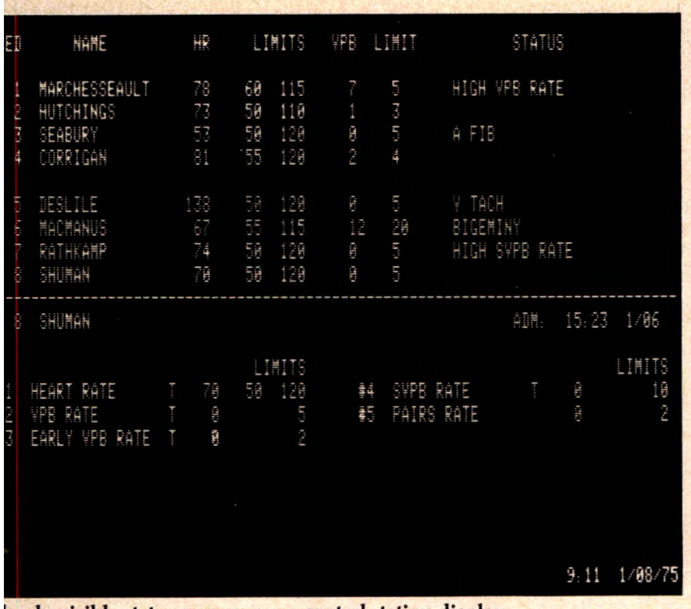
In addition, CMS can be added t any existing solid-trace B-D Electr dyne system, and may be purchase leased.

Obviously, there is much more t CMS than can be described in this space. To get details, send for CMS Booklet and abstract of an indepen ent clinical evaluation. B-D Electro dyne, Division of Becton, Dickinso and Company, Sharon, MA 02067. 617-828-9080.

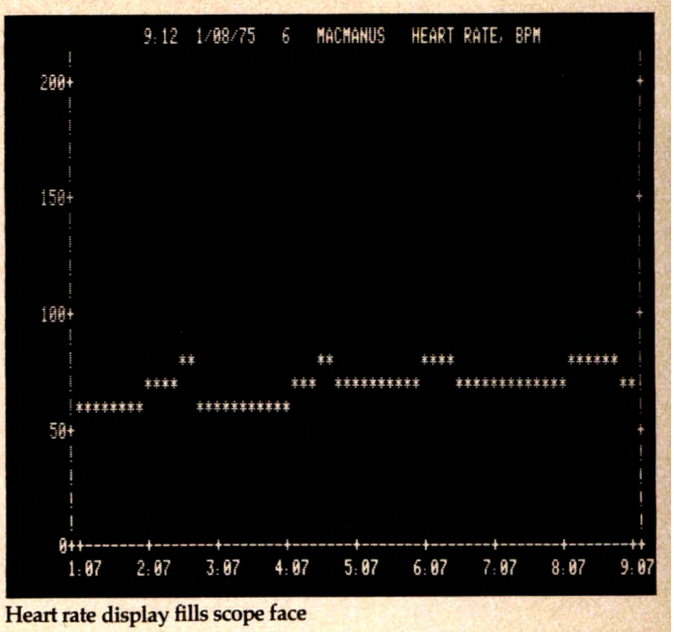
B-D **ELECTRODYNE**
Division of Becton, Dickinson and Company



neaning to monitoring.

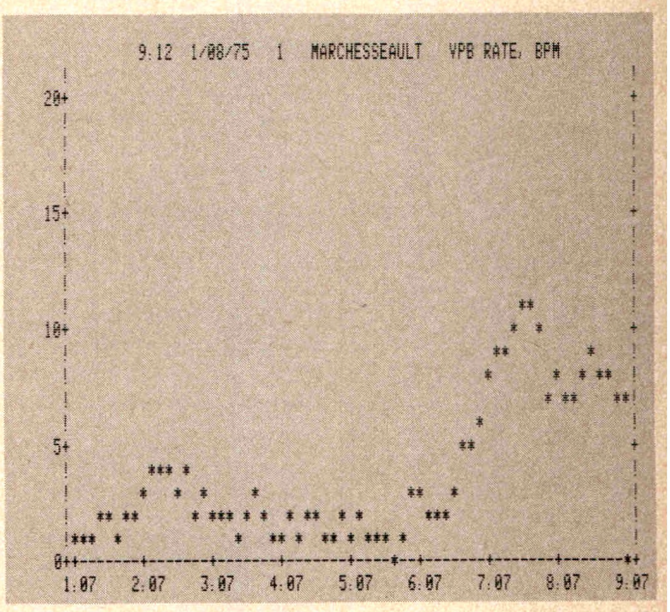


learly visible status summary on central station display



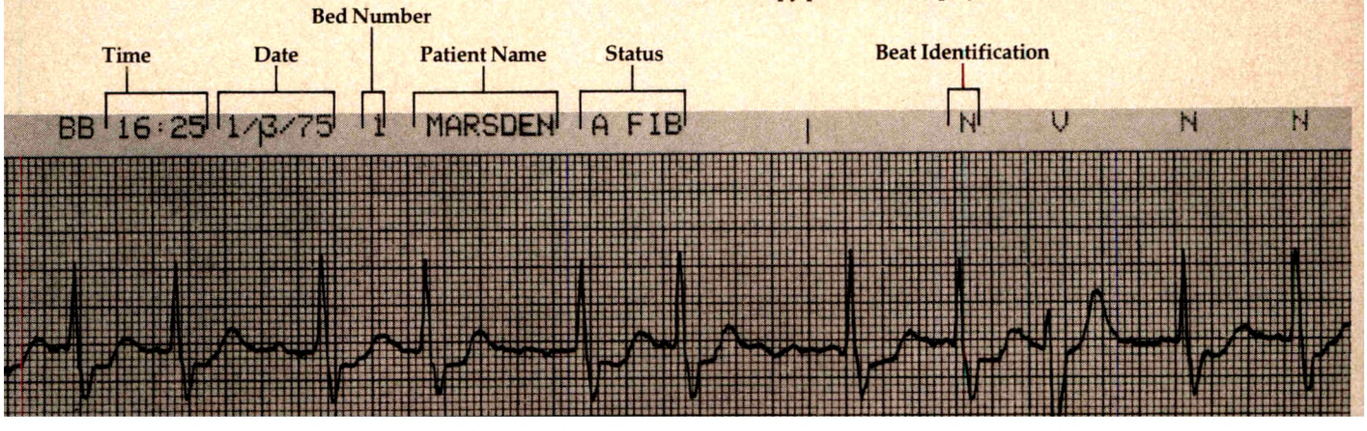
Heart rate display fills scope face

Ongoing record of status, trends
Large, easily readable displays for any variable being monitored. Can also be printed for permanent record.



Hard-copy printout of displayed VPB trend graph

Automatically labeled stripchart
ECG or blood pressure waveform and alphanumeric patient information. Automatically initiated at alarm condition. Can also be manually controlled.



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Peritrate® SA Sustained Action

(pentaerythritol tetranitrate) 80mg

CAUTION: Federal law prohibits dispensing without prescription.

Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later. Tablets should not be chewed.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also in unit dose—package of 10 x 10 strips (N 0047-0004-11).

Additional Dosage Forms: Peritrate 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also in unit dose—package of 10 x 10 strips (N 0047-0001-11). Peritrate 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

Defense against attack.

For over 22 years, Peritrate® has been considered by many physicians as one of the top defensive measures for patients with angina pectoris. In many patients Peritrate used prophylactically helps decrease the frequency and severity of angina attacks.* With minimal side effects.

Peritrate can also help reduce nitroglycerin requirements and, therefore, nitroglycerin side effects. Is it any wonder so many physicians continue to prefer Peritrate prophylaxis for their angina patients?

LONG-ACTING PROTECTION AGAINST ANGINA PAIN*

Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) 80 mg

Warner/Chilcott
Div. Warner-Lambert Company
Morris Plains, N.J. 07950
PE-GP-51

The Great Wall of China, an immense 1,400-mile-long man made barrier 20 to 30 feet high and 15 to 20 feet thick, helped defend China from the attack of Mongol hordes for more than 2,000 years.

*The drug has been evaluated as possibly effective for this indication.
See brief summary

now, one station does it all... collects ECG data, computes, analyzes, prints report

in minutes, at bedside, without central computer or telephone tie-ins

The Roche Mobile Computerized ECG Station contains its own minicomputer, recorder, and printer. It can eliminate the routine work associated with the reading of normal ECG's. It is highly accurate, classifying correctly 95-98% of normal ECG's, 85% of abnormals.[1] It is fast, supplying a computer printout based on the widely accepted USPHS program within a minute after readings are taken.

There is a high degree of patient safety. Also, the Roche Station signals the operator immediately when tracings are being taken incorrectly or are of poor quality; it identifies interpretations that may be incomplete or equivocal.

The Roche Mobile Station offers considerable savings over telephone tie-in ECG systems and yet avoids the extensive investment required for a dedicated central computer. Economic feasibility studies and additional information are available from Roche.

1. Hochberg, H. M., et al.: Automatic electrocardiogram analysis in rapid mass screening. *Arch. Environ. Health* 15:390-398, 1967.

For more information

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Schering

Stat regimen for rapid reduction of blood pressure in malignant hypertension

direct-action **Hyperstat®** I.V.
Brand of DIAZOXIDE
INJECTION
20 ml. ampule
contains 300 mg

"The injection of the [diazoxide] bolus in 10 to 15 seconds results in a prompt blood pressure fall in a high percentage of cases. A maximal blood pressure response usually occurs within 5 to 10 minutes."*

☐ **Rapid reduction to normotensive levels**

Induces rapid reduction of blood pressure generally within 5 minutes... often in 1 or 2 minutes to the lowest level achieved. Blood pressure response facilitated by appropriate diuretic therapy.

☐ **Prolonged activity**

A single injection of HYPERSTAT I.V. generally maintains blood pressure below pretreatment levels for periods up to 12 hours.

☐ **Protective action—helps avert target organ damage**

Cardiac output increases as diastolic pressure is reduced. Coronary and cerebral blood flow maintained. Increased renal blood flow after transient decrease.

☐ **Uncomplicated procedure**

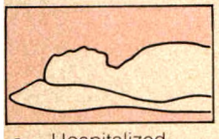
Simple I.V. "push" in a peripheral vein in 30 seconds or less. Close monitoring at frequent intervals is necessary until blood pressure is stabilized (generally 15-30 minutes). Thereafter, hourly measurement should be taken during the balance of effect.

☐ **Stable... convenient... no preparation**

HYPERSTAT I.V. Injection supplied in a 20 ml. ampule containing a stable solution of diazoxide 300 mg. ...ready to use.

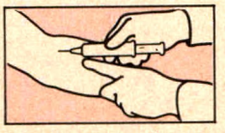
*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J* 87(6): 791-795, June 1974.

Administration guidelines



1. Hospitalized patient should be recumbent.

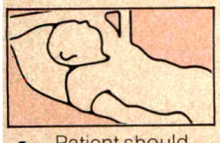
2. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml. ampule contains 300 mg. diazoxide).



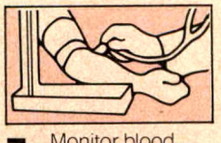
3. Insert needle only into a peripheral vein.

4. Inject entire dose I.V. in 30 seconds or less.

5. Remove needle carefully—avoid extravasation.

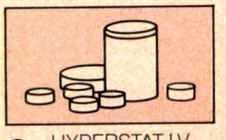


6. Patient should remain recumbent for at least half an hour after injection.



7. Monitor blood pressure closely until stabilized—usually 15-30 minutes.

8. If patient is to be ambulatory, blood pressure should be measured in standing position before surveillance is ended.



9. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective—generally within a few days.

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Before prescribing HYPERSTAT I.V. Injection, please consult complete product information on next page.

Stat regimen for rapid reduction of blood pressure in malignant hypertension

direct-action

Hyperstat® I.V.

Brand of DIAZOXIDE

INJECTION
20 ml ampule
contains 300 mg

FOR INTRAVENOUS USE IN HOSPITALIZED PATIENTS ONLY

Description HYPERSTAT I.V. Injection is a rapidly acting antihypertensive agent. Each ampule (20 ml.) contains 300 mg. diazoxide, a nondiuretic benzothiadiazine derivative, in a clear, colorless, aqueous solution; the pH is adjusted to approximately 11.6 with sodium hydroxide. Diazoxide is 7-chloro-3-methyl-2H 1, 2, 4-benzothiadiazine 1, 1-dioxide.

Actions HYPERSTAT I.V. Injection produces a prompt reduction in blood pressure by relaxing smooth muscle in the peripheral arterioles. Cardiac output is increased as blood pressure is reduced by diazoxide; coronary and cerebral blood flow are maintained. Renal blood flow is increased after an initial decrease. Diazoxide has no known direct action on the central nervous system.

Patients refractory to other antihypertensive agents usually remain responsive to diazoxide.

Diazoxide is extensively bound to serum protein (>90%). The plasma half-life is 28 ±8.3 hours; however, the duration of its antihypertensive effect is variable, generally lasting less than 12 hours. Although an antihypertensive response has been obtained with slow intravenous injection, in general, a greater antihypertensive effect is obtained with rapid intravenous administration.

Indications HYPERSTAT I.V. Injection is indicated for the emergency reduction of blood pressure in malignant hypertension in hospitalized patients, when prompt and urgent decrease of diastolic pressure is required. Treatment with orally effective antihypertensive agents should be instituted as soon as the hypertensive emergency is controlled.

HYPERSTAT (diazoxide) I.V. Injection is ineffective against hypertension due to pheochromocytoma.

Contraindications HYPERSTAT I.V. Injection should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt.

The drug should not be used in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

Warnings **Usage in Pregnancy:** The safety of HYPERSTAT I.V. Injection in pregnancy has not yet been established.

Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults.

Usage in Children: The safety of HYPERSTAT I.V. Injection in children has not yet been established.

Hypotension may occasionally result from the administration of HYPERSTAT I.V. If hypotension severe enough to require therapy occurs, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine.

Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide.

Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. It should be noted that concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions).

Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent.

Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

Precautions HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available when HYPERSTAT I.V. Injection is used.

HYPERSTAT I.V. Injection should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively.

Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response.

As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental.

Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection.

Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

Adverse Reactions

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial and/or cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; unconsciousness, convulsions, paralysis, or confusion; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported.

Other adverse reactions: Nausea, vomiting, and/or abdominal discomfort; vasodilative phenomena, such as flushing, generalized or localized sensations of warmth, headache (sometimes throbbing), and sweating; orthostatic hypotension, lightheadedness, and weakness of short duration; supraventricular tachycardia and palpitation; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; nonanginal "tightness in the chest"; warmth or pain along the injected vein; cellulitis without sloughing and/or phlebitis at the site of extravasation; anorexia and alteration of taste; ileus; bradycardia; back pain; chest discomfort; dyspnea, choking sensation; apprehension or anxiety, malaise, and blurred vision occurred on single occasions; parotid swelling, salivation, lacrimation; ringing in the ears; diarrhea and constipation; increased nocturia; euphoria.

Drug Interactions Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

Overdosage Overdosage of HYPERSTAT I.V. Injection may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy of hyperglycemia.

Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

Animal Pharmacology and Toxicology In studies involving a number of species, including the rat, cat, dog, and monkey, diazoxide has been shown to exert significant antihypertensive actions through its direct effect on peripheral arterioles, which neither impairs cardiac function nor seriously diminishes perfusion of kidneys. In addition, in each species tested, including the rat, dog, and monkey, diazoxide elicits hyperglycemia, increased serum-free fatty acids and decreased plasma insulin levels by a mechanism thought to involve both suppression of insulin release and enhanced catecholamine action.

Although the data are not conclusive, reproduction and teratology studies in several species of animals indicate that diazoxide, when administered during the critical period of embryo formation, may interfere with normal fetal development, possibly through altered glucose metabolism. Parturition was occasionally prolonged in animals treated at term.

Dosage and Administration HYPERSTAT I.V. Injection is administered undiluted and rapidly by intravenous injection. It should only be given into a peripheral vein. Do not administer it intramuscularly, subcutaneously, or into body cavities. Avoid extravasation of the drug into subcutaneous tissues.

The response to HYPERSTAT I.V. Injection varies from patient to patient. Generally, blood pressure decreases within five minutes, often within one to two minutes, to the lowest level achieved. The blood pressure increases relatively rapidly in the next ten to 30 minutes, and then more slowly over the following two to 12 hours, nearly reaching but rarely exceeding the pretreatment level. The response to successive injections is frequently better than that to the initial injection.

Treatment of hypertensive emergencies with HYPERSTAT I.V. Injection should be limited to a few days and a regimen of oral antihypertensive medications should be instituted as soon as possible.

With the patient recumbent, the contents of one 20 ml. ampule containing 300 mg. of HYPERSTAT I.V. Injection are administered intravenously in 30 seconds or less. Slow intravenous injection may fail to reduce the blood pressure or may produce an exceedingly short response.

Specific dosage is required in children or in unusually large or small patients. This dosage may be calculated on the basis of 5 mg./kg. body weight (0.3 ml./kg.) (See Warnings).

A second administration of HYPERSTAT (diazoxide) I.V. Injection may be required for a satisfactory reduction in blood pressure, if the first injection fails to give an adequate response within 30 minutes.

Repeated administration of HYPERSTAT I.V. Injection at intervals of four to 24 hours usually will maintain the blood pressure below pretreatment levels until a regimen of oral antihypertensive medication becomes effective. The interval between injections may be adjusted by the duration of the response to each injection. It is usually unnecessary to continue treatment with HYPERSTAT I.V. Injection for more than four to five days.

Following the use of HYPERSTAT I.V. Injection, the blood pressure should be monitored closely until it has stabilized. Thereafter, measurements taken hourly during the balance of the effect will indicate any unusual response. A further decrease in blood pressure at 30 minutes or more after injection should be investigated for causes other than the action of HYPERSTAT I.V. Injection. It is preferable that the patient remain recumbent for half an hour after injection. In ambulatory patients, the blood pressure should be measured with the patient standing before surveillance is ended.

Since repeated administration of HYPERSTAT I.V. Injection can lead to sodium and water retention, administration of a diuretic may be necessary both for maximal blood pressure reduction and to avoid congestive failure.

How Supplied HYPERSTAT I.V. Injection is supplied in a 20 ml. ampule containing diazoxide 300 mg. in a clear, colorless aqueous solution; box of one ampule.

Protect from light and freezing.

Store away from heat.

AUGUST 1973

20 ml.
in 30 seconds or less
for direct action

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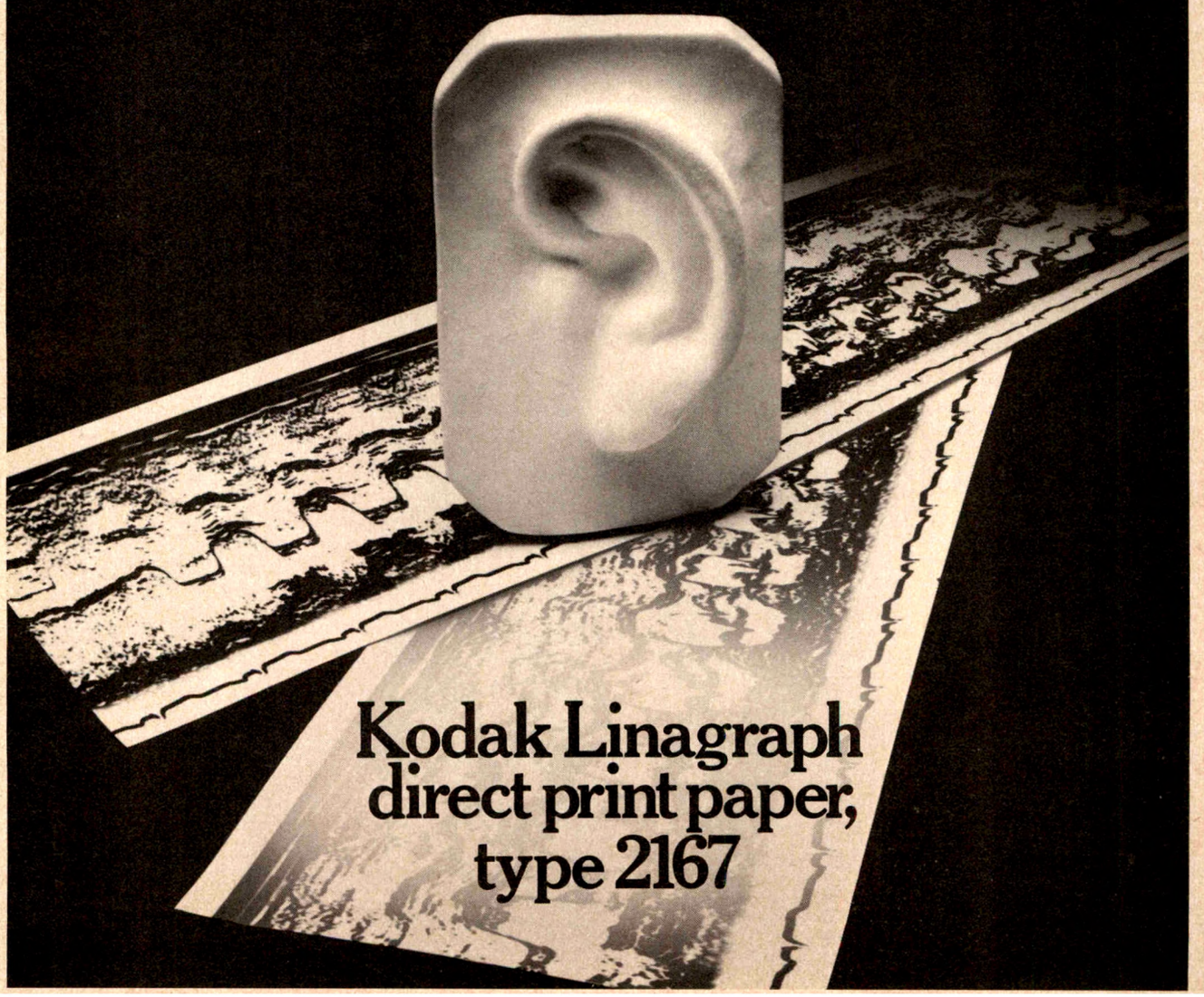

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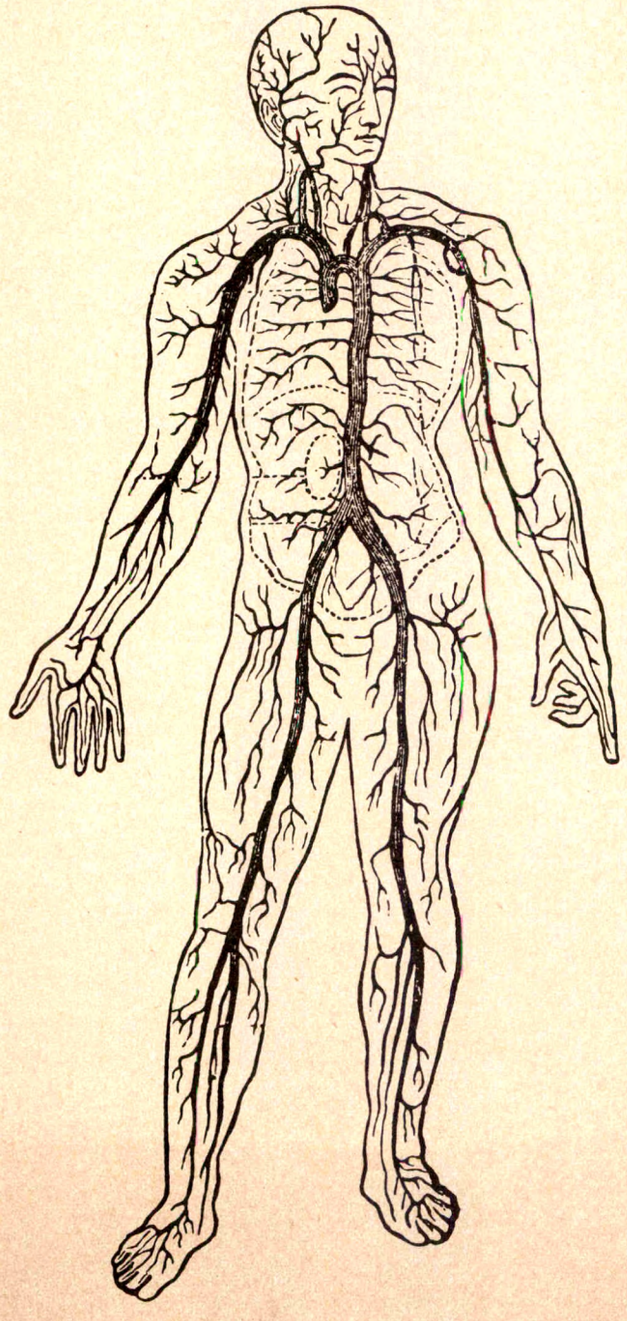

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Possibly effective:
For the management, prophylaxis or treatment of anginal attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Recent myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy, hypotension.
Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.
Adverse Reactions: Occasional transient headaches. Overdose may cause flushing, headaches, tachycardia, dizziness.
Dosage: One capsule two or three times daily at 8 to 12-hour intervals.

References:
1. Russek HI: What constitutes adequate medical therapy for the patient with angina pectoris? *Geriatrics* **29:**109-118, 1974.
2. Wendkos MH, Meshulam N: Comparative effects of placebo and sustained-release nitroglycerin in anginal subjects. *J Clin Pharmacol* **13:** 160-166, 1973.

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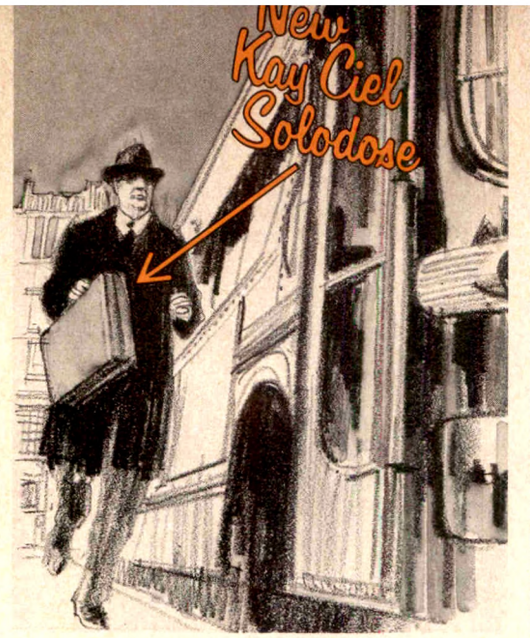

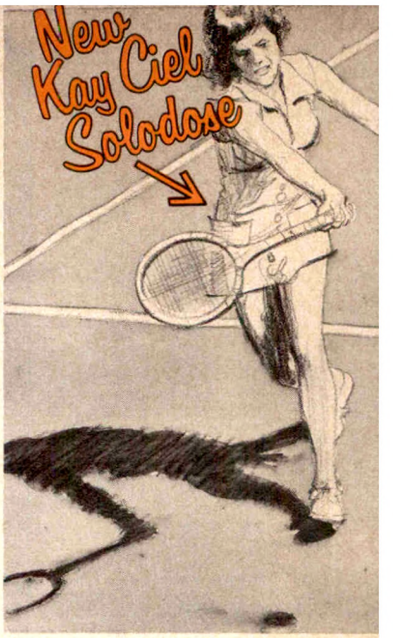

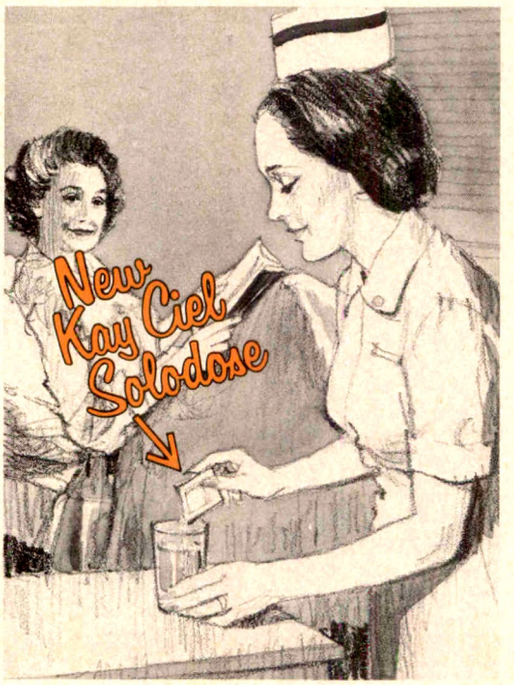

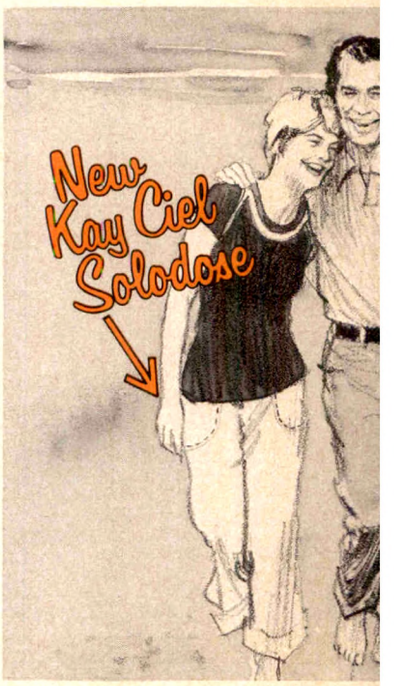

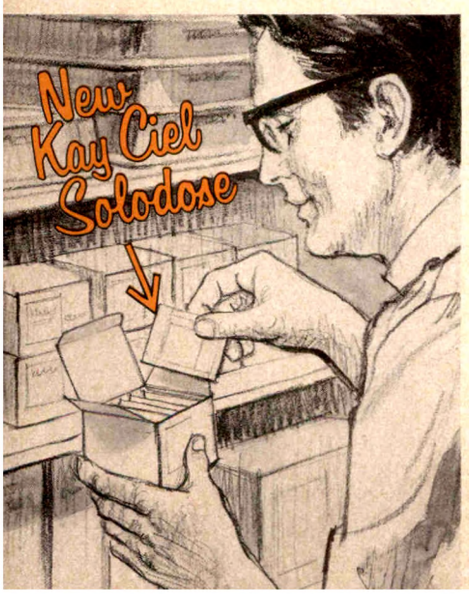

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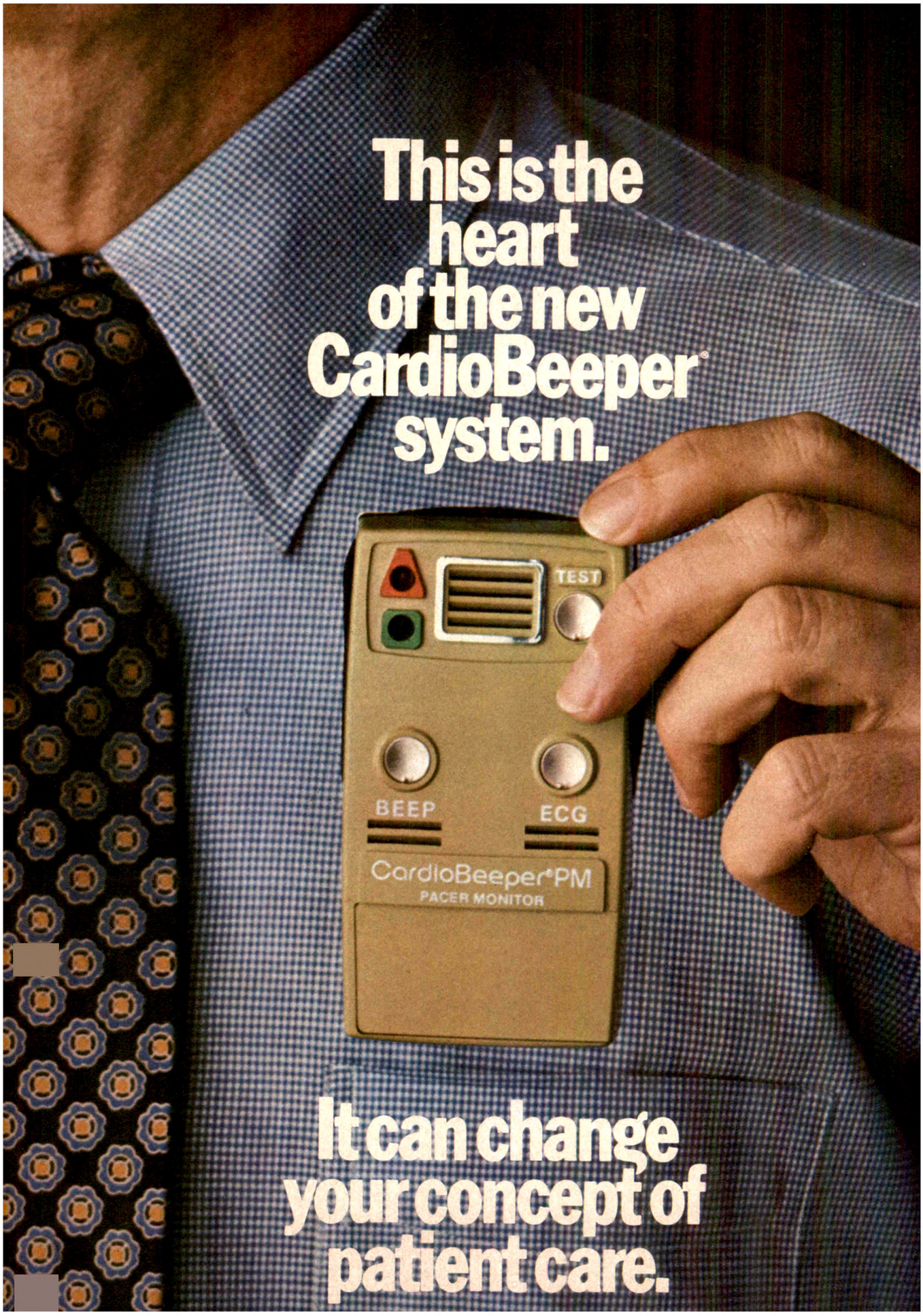
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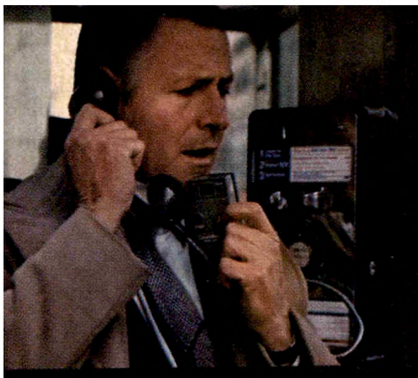

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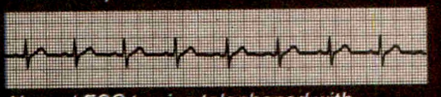

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CardioBeeper®
heart monitor

Wyeth Laboratories
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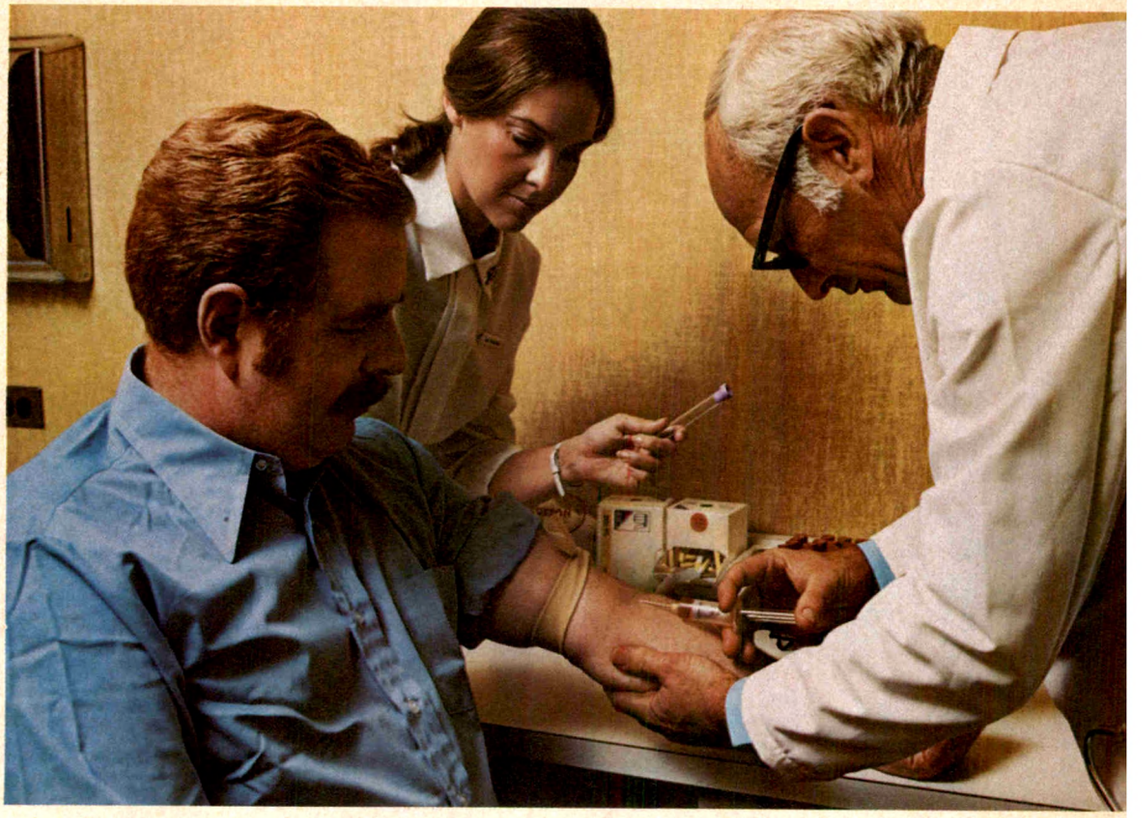
Survival Technology, Inc.

"Hyperlipidemia is one of several factors I sear



(Photographs profession

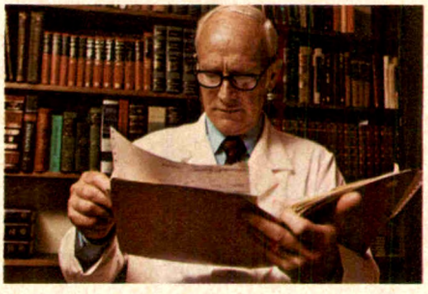
Complete lipid work-up should include both cholesterol and triglyceride determinations

Testing for both lipids—rather than just for cholesterol alone—increases the chances of detecting hyperlipidemia from 60% to over 95%.[2]

Lab results indicate pattern of lipid abnormality

When initial determinations of fasting serum cholesterol and triglyceride levels indicate the presence of hyperlipidemia, the pattern of the lipid abnormality should also be determined.[3]

When lipid elevations are confirmed, underlying disease states that may alter lipid metabolism should be ruled out through history, physical examination, and appropriate laboratory tests. Effective treatment of these pathologic conditions, if they exist, will often return the elevated lipids to a normal range. In the absence of an underlying cause, elevated lipid levels indicate a primary hyperlipidemia.



Therapy begins–but does not necessarily end–with specific dietary recommendations

Diet (specific for the lipid abnormality) is the starting point in the management of primary hyperlipidemia, and in the relatively rare Type I hyperlipop emia it is the *only* therapy since c available drugs are ineffective. B the drug-responsive types (Type IIb, III, IV and V) diet alone may lower lipids adequately.

Drug therapy is often necessary as an adjunct

Convincing the asymptomatic hy demic patient to give up his favo foods for benefits he may not fee best, a difficult task. Even under fully monitored dietary regimens reductions may be inadequate.[4] F reasons it is often necessary to ac antilipemic agent to the dietary r to produce a significant reductior serum lipids.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or li levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart dise Several years will be required before current investigations will yield an answer to this question.

or and vigorously treat."[1]

ng with early hypertension, excessive rette smoking and dietary indiscre- s, it is one of the few manifestations nodern society that an individual sician can attempt to control."[1]

his is how one clinician views hyper- lemia—a condition widespread in erica today. The treatment he speaks ften calls for a dietary regimen spe- for the lipid abnormality *plus* an lipemic agent. And since many hy- ipidemic patients exhibit elevations *oth* cholesterol and triglycerides, need a drug such as ATROMID-S fibrate), which has the ability to er *both* lipids.

omid-S significantly reduces lesterol and triglycerides—often in ents unresponsive to diet[5]

ATROMID-S as an adjunct to diet has oven record of effectiveness in lower- serum elevations of both cholesterol triglycerides.[5-8]

lthough most hyperlipidemic pa- ts are asymptomatic, a small number exhibit skin lesions or xanthomas. ression of xanthomatous lesions with OMID-S visually demonstrates the cacy of this lipid-lowering agent. In ie patients xanthomas disappear pletely. In others the size and num- of lesions are reduced.

tinuous treatment, maintenance of y dosage vital to long-term control

eliable cholesterol- and triglyceride-lowering effect is usually sustained as long as ATROMID-S treatment is uninterrupted. This ability to maintain control of serum lipids for extended periods is of primary importance in treating a disorder as persistent as hyperlipidemia.

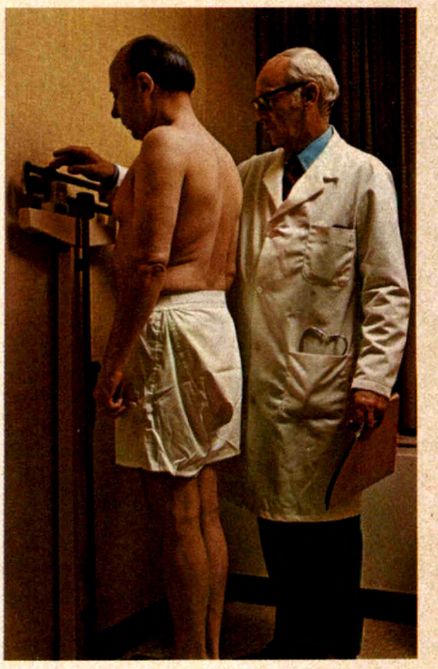
ATROMID-S is effective in a simple, well-accepted regimen that patients can stay with. Initial *and* maintenance dosage is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage. To maintain continuous control of lipid levels, therapy should be uninterrupted.

The lipid-lowering effect of ATROMID-S is usually noted during the first month of therapy. The higher the initial level, the greater the lipid reduction likely to occur.

If response is inadequate after three months of therapy, the drug should be discontinued. However, if xanthoma tuberosum is present, treatment should continue for longer periods (even up to one year) provided there is a reduction in the size and/or number of the xanthomas.

10 years of successful overall clinical experience with Atromid-S

Throughout more than ten years of widespread use, ATROMID-S has proven to be an effective and very well-tolerated drug. However, before prescribing, you should be thoroughly familiar with the possible adverse reactions as well as with the precautions and warnings described on the last page of this advertisement.



Periodic follow-up important

Once blood lipids have been stabilized at normal levels on a regimen of diet and ATROMID-S, the patient should be examined and his blood lipids tested every two to three months during the first year or so. If stabilization at such lower levels is maintained over this period, the intervals between measurements can be lengthened.

Atromid-S®

Brand of clofibrate

helps control the lipid factor in your patient's profile

Ayerst®

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

See last page of advertisement for prescribing information.

Atromid-S® (clofibrate)
helps reduce elevated cholesterol and/or triglyceride levels — not just cholesterol alone

Initial and maintenance dosage: 2 Gm. daily (four capsules), in divided doses. Some patients may respond to a lower dosage.

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® (clofibrate)

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients v a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soren cramping). The physician should differentiate this from actual viral and bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has b reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and m frequently, leukopenia have been reported in patients who have been tak clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may duce a decrease in cholesterol linoleate but an increase in palmitoleate oleate, the latter being considered atherogenic in experimental animals. significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common nausea. Less frequently encountered gastrointestinal reactions are vomit loose stools, dyspepsia, flatulence, and abdominal distress. Reactions repor less often than gastrointestinal ones are headache, dizziness, and fatigue; m cle cramping, aching, and weakness; skin rash, urticaria, and pruritus; brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, he turia, proteinuria, decreased urine output. One patient's renal biop suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transamina (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has r been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arth tis, tremors, increased perspiration, systemic lupus erythematosus, blurr vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage adults is 2 Gm. daily, in divided doses. Some patients may respond to a low dosage. *Maintenance:* Same as for initial dosage. **Note:** In children, insufficie studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulan are given in conjunction with ATROMID-S (clofibrate). The dosage of the ant agulant should be reduced usually by one-half (depending on the individu case) to maintain the prothrombin time at the desired level to prevent bleedi complications. Frequent prothrombin determinations are advisable until it h been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported ca of overdosage, should it occur, symptomatic supportive measures should taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg. cl brate, in bottles of 100.

References: 1. La Bree, J., M.D. (Director of Medical Education, St. Mary Hosp., Minneapolis, Minn.): Unraveling the Metabolic Mysteries Affecti Diagnosis and Therapy, Ayerst Laboratories, 1972, p. 13. 2. Fredrickson, D. *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R.: Drugs Affecting Lip Metabolism, New York, Plenum Press, 1969, vol. 4, p. 314. 3. Levy, R. I., Conn, H. F.: Current Therapy 1973, Philadelphia, Saunders, 1973, p. 2 4. Parsons, W. B., Jr.: Clin. Med. 78:15 (Nov.) 1971. 5. Gelfand, M. L., ar Garber, M.: Exhibit, American College of Cardiology Meeting, New Orlea La., Feb. 21-Mar. 1, 1970. 6. Berkowitz, D.: J.A.M.A. 218:1002 (Nov. 15) 19 7. Zelis, R., *et al.*: J. Clin. Invest. 49:1007 (May) 1970. 8. Levy, R. I., and Fr rickson, D. S.: Am. J. Cardiol. 22:576 (Oct.) 1968.

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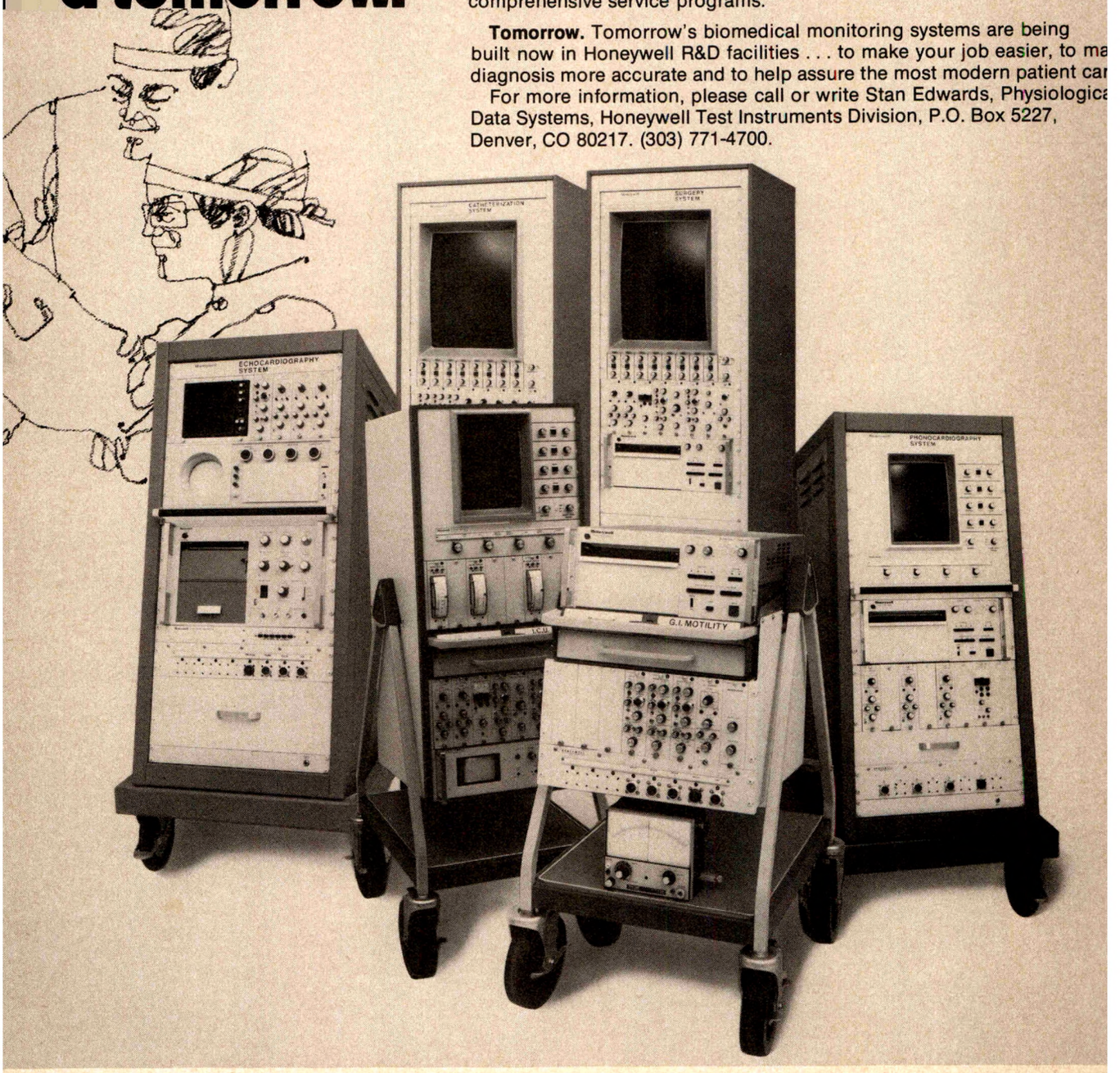

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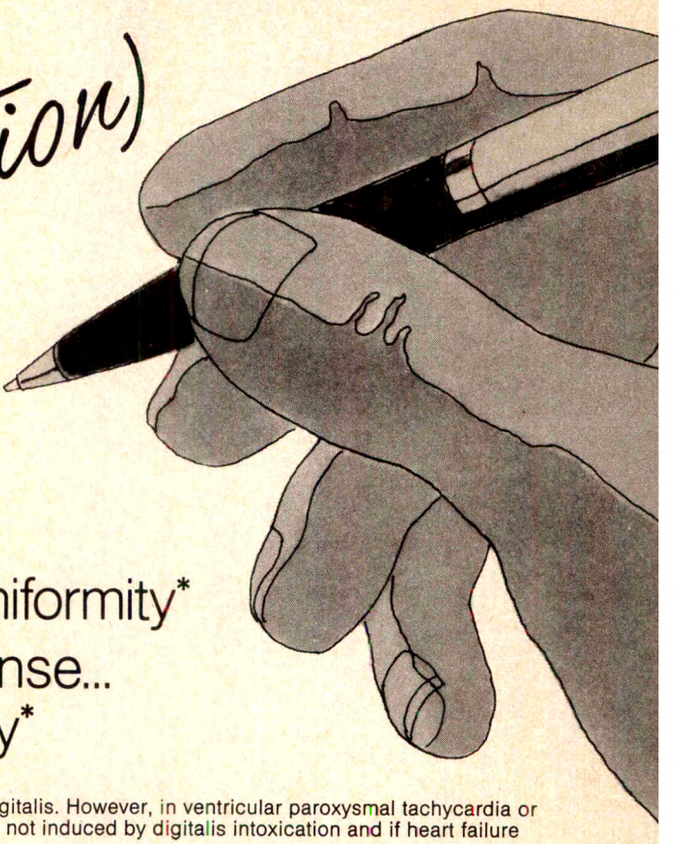

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precision quality control...
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Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

LANOXIN® digoxin TABLETS. **0.125 mg.** (yellow) in bottles of 100 and 1,000. **0.25 mg.** (white) scored, in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack, strips of 10 tablets, 10 boxes of 100 tablets (1,000). **0.5 mg.** (green) scored, in bottles of 100 and 1,000.

Lanoxin® digoxin

*Complete literature available on request from Professional Services Dept. PML.

Wellcome / **Burroughs Wellcome Co**
Research Triangle Park
North Carolina 27709

SEPTEMBER 1975

The American Journal of CARDIOLOGY®

VOLUME 36

NUMBER 3

CLINICAL STUDIES

New Observations on the Effects of Atropine on the Sinoatrial and Atrioventricular Nodes in Man

GOPAL DAS, MD, FACC
FREDERICK N. TALMERS, MD, FACC
ARNOLD M. WEISSLER, MD, FACC

Allen Park and Detroit, Michigan

Previous observations of slowing of the heart rate after administration of atropine in doses smaller than 0.4 mg and recent reports of development of rhythm disorders in patients with acute myocardial infarction given atropine prompted us to evaluate systematically the effects of various doses of atropine (0.1 to 0.8 mg) on the response of the sinoatrial (S-A) and atrioventricular (A-V) nodes in healthy volunteers. The response of the S-A node to atropine was characteristically bimodal, slowing at smaller doses and accelerating at larger doses. In contrast, the A-V node showed acceleration of conduction in response to all doses of atropine used. A hypothesis based on current understanding of the electrophysiologic parameters governing impulse formation and impulse conduction is advanced to explain the apparent paradox in the S-A and A-V nodal responses to small doses of atropine. The results suggest the need for caution and continuous rhythm monitoring when giving atropine to patients with acute myocardial infarction.

The function of the sinoatrial (S-A) and atrioventricular (A-V) nodes is influenced by a balance between parasympathetic and sympathetic control mechanisms. Stimulation of the parasympathetic system causes a decrease in the S-A nodal rate and prolongation of A-V conduction time.[1] On the other hand, blockade of parasympathetic influences results in an increase in the S-A rate and abbreviation of A-V conduction time. Previous observations have shown that atropine, an agent well known for its vagolytic action in usual doses, in fact decreases the cardiac rate in small doses.[2] This study was designed to evaluate the pharmacologic effects of atropine in doses ranging from 0.1 to 0.8 mg on the S-A and A-V nodes in man. Since A-V conduction is influenced by changes in heart rate as such, the effects of atropine on A-V conduction time were further studied in patients whose heart rate was maintained constant by atrial pacing.

Material and Methods

The study was carried out in normal volunteer subjects aged 25 to 35 years and in patients undergoing diagnostic atrial pacing studies. Informed consent was obtained from each person. None of the normal subjects had cardiac ab-

From the Veterans Administration Hospital, Allen Park, Mich. and Wayne State University School of Medicine, Detroit, Mich. Manuscript accepted November 26, 1974.

Address for reprints: Gopal Das, MD, Cardiovascular Research Laboratory, Veterans Administration Hospital, Allen Park, Mich. 48101.

TABLE I

Effects of Intravenous Administration of Placebo and Atropine on S-A Nodal Rate and A-V Conduction Time (mean ± standard error of the mean)

Drug	Subjects per Group	Control	After Drug	Change	Significance
		S-A Nodal Rate (beats/min)			
Placebo	17	67.7 ± 1.9	67.7 ± 1.9	0 ± 0.7	NS
Atropine					
0.1 mg	11	71.0 ± 3.8	64.8 ± 3.1	−6.2 ± 1.1	$P < 0.001$
0.2 mg	14	68.1 ± 2.1	62.1 ± 1.8	−5.9 ± 0.8	$P < 0.001$
0.3 mg	9	71.8 ± 4.4	68.4 ± 4.1	−3.3 ± 2.2	$P < 0.2$
0.4 mg	16	65.8 ± 2.6	66.9 ± 2.7	+1.1 ± 1.6	NS
0.8 mg	12	69.8 ± 3.8	91.2 ± 4.8	+21.4 ± 3.0	$P < 0.001$
		A-V Conduction Time (msec)			
Placebo	17	150 ± 4.1	149 ± 3.5	−0.9 ± 1.3	NS
Atropine					
0.1 mg	11	158 ± 4.6	151 ± 6.2	−7 ± 1.6	$P < 0.001$
0.2 mg	14	157 ± 6.1	141 ± 5.6	−16 ± 2.6	$P < 0.001$
0.3 mg	9	163 ± 7.0	142 ± 6.8	−21 ± 2.4	$P < 0.001$
0.4 mg	16	161 ± 5.3	143 ± 5.3	−18 ± 2.2	$P < 0.001$
0.8 mg	12	149 ± 5.4	137 ± 4.6	−12 ± 3.3	$P < 0.01$

NS = not significant; P = probability.

normalities as detected on physical examination, chest X-ray film or electrocardiogram. The patient studies were carried out from a protocol identical to that for normal subjects except that a bipolar pacing electrode was positioned near the junction of the superior vena cava and right atrium under fluoroscopic monitoring and the right atrium was continuously paced with a 2 msec square wave pulse of twice the threshold amplitude (Medtronic model 5837 pulse generator). The heart rate in these patients was held constant at 100 to 110 beats/min throughout the period of atropine administration.

For all studies, an intravenous infusion with 5 percent dextrose in water was started and surface electrocardiographic leads were applied and connected to a DR-8 (Electronics for Medicine) recorder. Each subject was then allowed to rest for 30 minutes before the study. Three electrocardiographic leads (I, II and aVF) were simultaneously displayed and recorded at a paper speed of 100 mm/sec with time lines at 40 msec intervals. Three control recordings were obtained 10 minutes apart and the results averaged. Placebo (1 ml of normal saline solution) or atropine (diluted in 1 ml of saline solution) was administered by intravenous tubing over a period of 1 minute in a single blind manner. The tracings were then repeated 5 minutes later. The S-A nodal rate was derived from mean P-P intervals and was rounded to the nearest integer, and the A-V conduction time was measured from the beginning of the P wave to the beginning of the QRS complex and was expressed to the nearest 4 msec. Ten to 20 beats were measured and averaged for each determination. Student's paired t test was used to analyze the statistical significance of the data.

Results

The effects of atropine on the S-A nodal rate and A-V conduction time are summarized in Table I and Figure 1. Both were essentially unchanged after administration of placebo. Atropine in doses smaller than 0.4 mg caused slowing of the S-A rate. With increasing doses above 0.4 mg there was a sequential increase in sinus rate. In contrast, A-V conduction time decreased progressively at all dose levels used.

The response of A-V conduction time when the heart rate was held constant by atrial pacing consisted of a progressive abbreviation throughout the range of atropine doses used (Fig. 2).

Discussion

Pharmacology of atropine: Although atropine was isolated by Vaquelin[3] in 1809, it was Bezold and Bloebaum[4] who demonstrated its antivagal properties in 1867. Stimulation of the parasympathetic nervous system leads to release of acetylcholine at postganglionic parasympathetic nerve endings (muscarinic effects) and at preganglionic nerve endings (nicotinic effects).[5] In therapeutic doses (0.4 to 1.0 mg) atropine modifies the muscarinic effects alone,[4,6] whereas in large doses it blocks both the muscarinic and the nicotinic effects of acetylcholine.[7] However, there is a considerable variation in the response to atropine depending on the organ system.[8] Although in therapeutic doses atropine effectively blocks the effects of vagal stimulation on the heart and salivary glands, the effects on the intestinal and urinary bladder musculature remain intact.[8,9] The mechanism of atropine action is not clearly understood although it is widely believed to be the competitive inhibition of the parasympathetic receptors. The secretion of acetylcholine from nerve endings is not affected.[10,11] The effects of atropine begin about 25 seconds after intravenous injection and reach a peak value in 2 to 3 minutes.[12]

Effects of atropine on S-A and A-V nodes: It has been well established that stimulation of the parasympathetic system causes a decrease in S-A

TABLE II

Possible Mechanisms of Slowing of S-A Nodal Rate in Response to Small Doses of Atropine

1. Central stimulation of vagal centers[1,19–23]
2. Peripheral stimulation of parasympathetic receptors[4,26]
3. Inhibition of cholinesterase enzyme[27,29]
4. Effects on sympathetic nervous system[30]
5. Direct effects on the pacemaker cells

rate and a prolongation of A-V conduction time.[1] Pharmacologic blockade, on the other hand, results in an increase in S-A rate and an abbreviation of A-V conduction time. The magnitude of these responses depends upon the degree of endogenous parasympathetic activity at the time of drug administration. Atropine in therapeutic doses induces acceleration of the S-A rate and a decrease in the A-V conduction time as evidenced by the P-R interval. However, as shown herein and by others,[13–18] small doses of atropine (less than 0.4 mg) actually slow the S-A rate whereas, as demonstrated in this study, A-V conduction accelerates consistently (Table I). In normal subjects (Fig. 1) there was a lesser abbreviation of A-V conduction time after administration of 0.8 mg of atropine than after administration of 0.4 mg. We believe that this represents the secondary effects of the acceleration in heart rate induced at the higher dose level (Table I: no significant change in heart rate at 0.4 mg, an increase of 21 beats at 0.8 mg). When heart rate was maintained constant by atrial pacing, A-V conduction time decreased progressively with increasing doses of atropine (Fig. 2), lending evidence that the acceleration of A-V conduction is indeed dose-dependent throughout the range of doses studied.

Mechanism of S-A slowing with small doses of atropine: The explanation for the differential effects of atropine on the S-A and A-V nodes is not clear. In the past, various mechanisms have been proposed to explain the vagotonic effects of small doses of atropine on the S-A node (Table II). Atropine in small doses causes stimulation of the central nervous system,[19,20] particularly of the medulla oblongata,[1] resulting in stimulation of vagal centers. According to Mitchell,[21] Szerb[22] and Polak,[23] the release of acetylcholine within the central nervous system is responsible for the increased central vagal tone. That this mechanism cannot be the sole explanation for the slowing in heart rate is evidenced by the observation of Kottmier and Gravenstein[24] that the bradycrotic response following administration of small doses of atropine persisted after bilateral vagotomy. Furthermore, atropine methylbromide, which does not cross the blood brain barrier, induces cardiac slowing when administered in small doses.[24,25]

In relation to the intrinsic mechanics of atropine at peripheral nerve endings Lullman et al.,[26] Sekiya[27] and Kato[28] demonstrated that atropine inhibits the activity of the enzyme cholinesterase, and they postulated that in small doses this anticholinesterase activity may actually predominate and lead to an increased receptor response to naturally existing acetylcholine.

Another explanation of the slowing of S-A rate is that vagotonic effects of atropine may exert their influence through inhibition of the sympathetic nervous system or beta adrenergic receptors in the heart. Studies by Malhotra and Das[29] revealed increased release of acetylcholine to parasympathetic stimulation in the presence of sympathetic blockade. However, Chamberlain et al.[30] found persistence of cardiac slowing after administration of atropine in volunteers

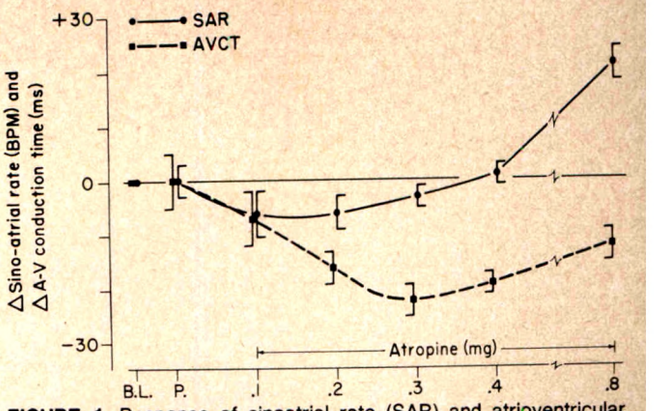

FIGURE 1. Response of sinoatrial rate (SAR) and atrioventricular conduction time (AVCT) to increasing dosage of atropine. B.L. = base-line (control) value; BPM = beats/min; ms = milliseconds; P. = value with placebo. Data expressed as mean values ± standard error of the mean.

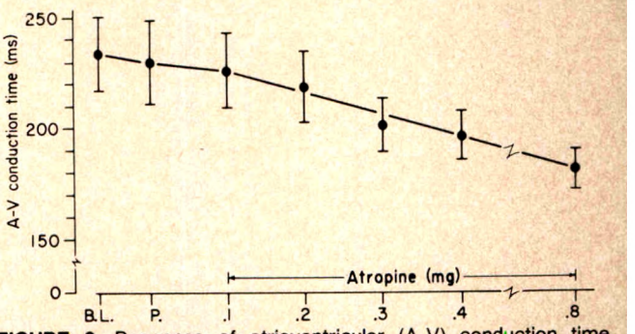

FIGURE 2. Response of atrioventricular (A-V) conduction time, under conditions of constant heart rate produced by atrial pacing, to increasing dosage of atropine. B.L. = base-line (control) value; P. = value with placebo. Data expressed as mean values ± standard error of the mean.

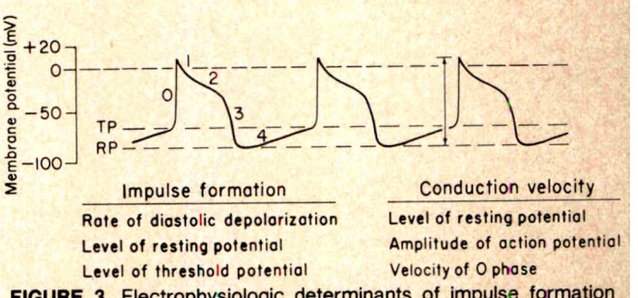

FIGURE 3. Electrophysiologic determinants of impulse formation and impulse conduction. RP = resting potential; TP = threshold potential.

in whom the beta receptors were blocked by propranolol, thus discounting sympathetic inhibition as a mechanism for this cardiac slowing.

According to Patton,[31] most receptor blocking agents in small doses produce brief depolarization of the receptors, resulting in stimulation, whereas large doses, by sustained depolarization, cause receptor blockade. In this respect the receptor stimulation after administration of small doses of atropine is comparable to the actions of ergot alkaloids on alpha adrenergic receptors and of dichloroisoproterenol and propranolol on beta receptors.[4]

Mechanism of effects of atropine on A-V conduction: Although the vagotonic response of the S-A node to small doses of atropine may be attributed to the peripheral mechanisms, the vagolytic response of the A-V node to the same doses of atropine remains unexplained. Recent knowledge of the electrophysiology of the cells in the S-A and A-V nodes and the electrophysiologic variables governing the function of these cells, namely, impulse formation and impulse conduction, may offer an explanation for these differences. According to current concepts (Fig. 3), the rate of impulse formation is related to the rate of diastolic depolarization (phase 4), the level of resting potential and the level of threshold potential.[32] If the difference between the resting potential and the threshold potential is increased either by increased resting potential (more negative) or by decreased threshold potential (less negative), the rate of impulse formation decreases. A decrease in the rate of phase 4 depolarization will also result in slowing of the rate of impulse formation. Impulse conduction, on the other hand, is critically related to the rate of rise of zero phase depolarization and the amplitude of the action potential, both of which are directly related to the magnitude of the resting potential of the cell.[33,34]

The effects of small doses of atropine, either by virtue of direct receptor stimulation or by anticholinesterase activity, would be similar to those of small doses of acetylcholine, namely, hyperpolarization (increased resting potential) of the cells and decreased rate of phase 4 depolarization,[32,35] resulting in a decreased rate of impulse formation (S-A node) and at the same time improved impulse conduction. Thus, one need not postulate actual differences in the actions of atropine on S-A and A-V nodal function; rather, the inherently unique electrophysiologic variables governing the function of these tissues would in themselves result in what appears to be a paradoxical response at small doses.

Clinical implications: One of the principal uses of atropine in cardiovascular practice is in the management of patients with a slow heart rate. Han et al.[36] have shown that excessive slowing of the heart rate results in a greater disparity in the duration of action potentials and the refractory periods of cardiac tissues. This inhomogeneous electrical setting predisposes to reentrant excitation and arrhythmias. Increasing the heart rate, on the other hand, decreases this inhomogeneity and the incidence of arrhythmias. This, along with recent observations emphasizing the high rate of occurrence of atropine-responsive bradycardia in patients with acute myocardial infarction,[37–39] and the high risk of serious arrhythmias and mortality in them,[40,41] has led to widespread recommendations for the use of large doses of atropine (1 to 2 mg) in the management of such patients.[37,42,43] Prophylactic use, including self-medication with atropine in the prehospital care of acute infarction, has been advocated to reduce the risk of these bradyarrhythmias.[44–46]

Although the systematic response of patients with acute myocardial infarction to graded doses of atropine is not known, our observations suggest caution in the use of atropine in such patients. Smaller doses may aggravate bradycardia, and larger doses may actually precipitate tachyarrhythmias.[47,48] We believe that greater vigilance and the titration of individual dosage during rhythm monitoring are mandatory in order to achieve an optimal response to atropine in such patients.

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Induction of Atrioventricular Nodal Reentrant Tachycardia After Atropine

Report of Five Cases

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After intravenous administration of 0.5 mg of atropine sustained atrioventricular (A-V) nodal reentrant tachycardia could be produced in five patients who had no prior historical or electrocardiographic evidence of supraventricular tachycardia. During the control period single atrial echo beats could be demonstrated in four of the five patients, but no instance of sustained tachycardia occurred. Atropine, known to enhance A-V nodal conduction, allowed achievement of longer A-H intervals (Case 1) and provided the necessary balance of conduction and refractoriness within the A-V nodal reentrant pathways (Cases 1 to 5) to sustain A-V nodal reentry in these patients.

It has repeatedly been observed that a critical degree of atrioventricular (A-V) nodal conduction delay is required for the demonstration of manifest A-V nodal reentry and the initiation of A-V nodal reentrant supraventricular tachycardia.[1–10] This critical degree of A-V nodal delay can be achieved either with appropriately timed premature atrial beats occurring during the relative refractory period of the A-V node or with rapid atrial pacing.[9] Less well appreciated is the fact that sustained A-V nodal reentry requires a critical balance between conduction and refractoriness within the reciprocating limbs of a reentrant circuit.

During the conduct of previous studies[11,12] designed to evaluate the effects of atropine on A-V conduction and refractoriness, we encountered five patients who had only single or no atrial echo beats due to A-V nodal reentry during the control period but who had sustained A-V nodal reentrant tachycardia after administration of small doses of atropine (0.5 mg intravenously). We postulate that atropine, known to enhance A-V nodal conduction, permitted the necessary balance of conduction and refractoriness to allow sustained reentrant tachycardia in these patients. This report deals with the observations made in these five patients.

Methods

Right heart catheterization was performed with patients under local anesthesia and in the postabsorptive, nonsedated state. The nature of the procedure was explained to all patients and signed consent was obtained. Electrode catheters were percutaneously introduced into peripheral veins and fluoroscopically positioned to record atrial and His bundle electrograms as previously described.[13] Atrial pacing was accomplished using a digital stimulator capable of delivering rectangular impulses of 1.5 msec duration at an adjustable milliamperage. The rate of atrial pacing was gradually increased (in increments of 10 beats/min) to rates sufficient to produce A-V nodal Wenckebach cycles. During pacing-induced A-V nodal Wenckebach cycles, the stimulator was periodically turned off to permit observation of subsequent spontaneous events. The atrial extrastimulus technique was employed to determine refractory periods of the A-V conduction system.[14] A premature

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atrial beat (A_2) was introduced after every eighth sinus or paced beat (A_1-A_1) until atrial refractoriness occurred.

Standard electrocardiographic leads I, II, III and V_1, intracardiac electrograms and time lines generated at 10 and 100 msec were displayed on a multichannel oscilloscope and recorded on magnetic tape. The records were subsequently recorded on photographic paper at a speed of 150 mm/sec. After completion of the control studies 0.5 mg of atropine was given intravenously and the studies were repeated 10 minutes after drug administration. All equipment was carefully grounded. The procedure was well tolerated by all patients.

Definition of Terms[15,16]

The A-H interval was measured from the onset of the low atrial electrogram (on the recording of the His bundle electrogram) to the beginning of the His bundle deflection and was used as an approximation of A-V nodal conduction time (normal for our laboratory 60 to 140 msec).

The H-V interval was similarly measured from the onset of the His bundle deflection to the beginning of ventricular activation and was taken as an approximation of His-Purkinje conduction time (normal for our laboratory 30 to 55 msec).

The effective refractory period of the atrium is defined as the longest S_1-S_2 interval in which S_2 fails to depolarize the atrium, S representing the artificial stimulus.

The effective refractory period of the A-V node is the longest atrial coupling interval (A_1-A_2 interval) in which A_2 blocks in the A-V node.

The functional refractory period of the A-V node is the shortest H_1-H_2 interval in response to a full range of A_1-A_2 intervals to the point of atrial refractoriness.

Atrial echo beat (A-V nodal reentrant atrial echo beat, Ae) is the reentrant atrial beat with a low to high sequence of atrial activation following induced atrial beats associated with a critical degree of A-V nodal conduction delay (A-H interval).

Results

Clinical and electrophysiologic data are summarized in Tables I and II. None of the patients had a history suggestive of tachycardia or electrocardiographic evidence of a supraventricular tachyarrhythmia or the Wolff-Parkinson-White syndrome. No patient was taking any cardioactive medications. The well known effects of atropine on sinus rate and A-V nodal conduction were observed in all five patients. The average decrease in sinus cycle length after administration of atropine was 164 msec (range 60 to 300 msec), representing an average decrease of 21 percent from control values. All patients manifested a decrease in the sinus A-H interval after administration of atropine (average decrease 28 msec). Results obtained in individual patients are as follows:

Case 1 (Fig. 1 and 2): In this 15 year old boy with first degree heart block of uncertain origin neither atrial echo beats nor A-V nodal reentrant tachycardia could be elicited during control studies but could readily be induced after administration of 0.5 mg of atropine. During control studies (Fig. 1, panels A and B) the longest A-H interval that could be achieved during premature atrial stimulation was 280 msec (panel A). The effective refractory period of the

TABLE I

Clinical Data

Case no.	Age (yr) & Sex	Diagnosis of Heart Disease	Resting Electrocardiogram
1	15M	None	1° A-V block, normal QRS complex
2	60M	Arteriosclerotic	Anterior myocardial infarction; right bundle branch block; left anterior hemiblock
3	75M	Arteriosclerotic	Left bundle branch block
4	56M	None	Normal
5	60F	None	Normal

TABLE II

Electrophysiologic Data (msec) Before (B) and After (A) Administration of Atropine

Case no.	State	Sinus Rhythm		Critical A-H Interval		Longest A-H Interval	
		Cycle Length	A-H Interval	For Atrial Echo Beats	For Supraventricular Tachycardia	During Continuous Atrial Pacing	During Antegrade Refractory Periods
1	B	680	250	—	—	290	280
	A	620	165	420	440–575	365	575
2	B	900	100	370–390	—	405	390
	A	600	85	275–285	275–400	400	285
3	B	780	105	295–465	—	465	400
	A	600	85	—	300–380	380	350
4	B	850	70	240–260	—	240	260
	A	650	60	—	240–260	260	150
5	B	680	100	430–600	—	560	600
	A	600	90	500	500–600	600	300

A-V node was determined to be 580 msec (panel B). After administration of atropine (panels C and D) the effective refractory period of the A-V node significantly shortened, thereby permitting more premature atrial beats to be conducted with longer A-H intervals. Sustained A-V nodal reentrant tachycardia consistently occurred after A-H intervals of 440 to 575 msec. Termination of tachycardia by a single properly timed premature atrial depolarization is illustrated in Figure 2.

Case 2 (Fig. 3): In the control period, only infrequent single atrial echo beats occurred after A-H intervals of 370 to 390 msec induced by premature atrial stimulation; these beats did not occur at similar A-H intervals during pacing-

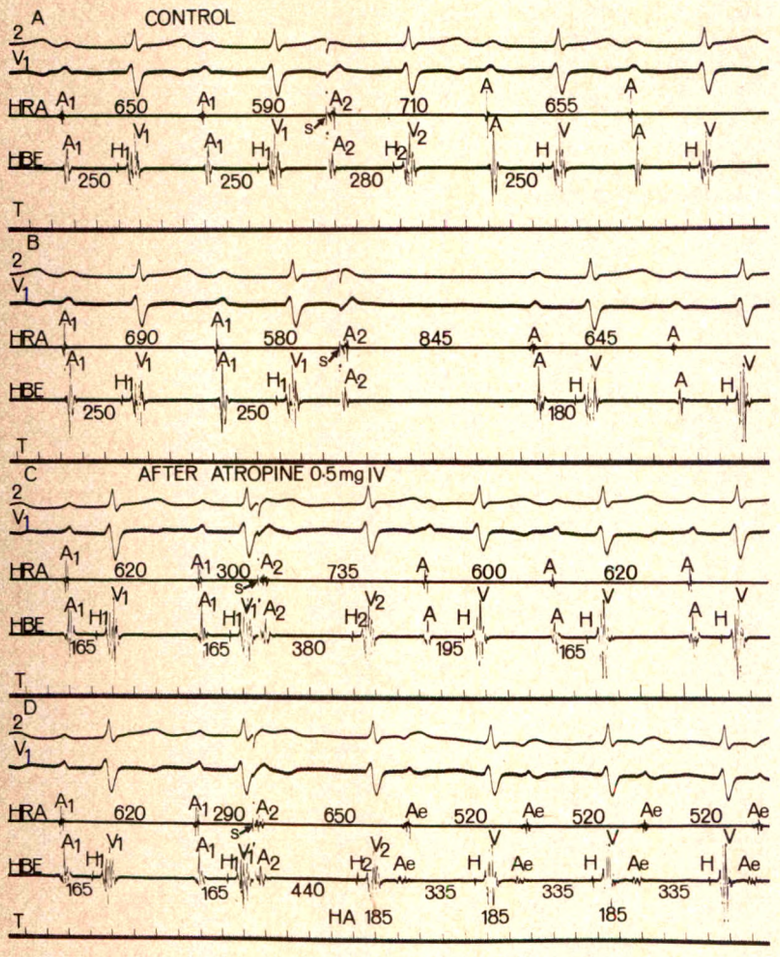

FIGURE 1. Case 1. Supraventricular tachycardia after administration of atropine. Tracings in each panel **(from top to bottom)** are: electrocardiographic leads II (2) and V_1, a high right atrial electrogram (HRA), His bundle electrogram (HBE) and time lines (T) at 10 and 100 msec. S denotes stimulus artifact. During sinus rhythm the A-H interval is abnormally prolonged at 250 msec and the sequence of atrial activation is from the high to the low atrium. In the control period a premature atrial beat (A_2) coupled to a preceding sinus beat (A_1) at an interval of 590 msec is conducted with an A_2-H_2 interval of 280 msec. At a slightly closer A_1-A_2 interval of 580 msec **(panel B),** A_2 is blocked in the A-V node and a sinus escape beat follows. Administration of atropine resulted in shortening of the sinus cycle length and the A-H interval and a marked decrease in the effective refractory period of the A-V node as evidenced by the ability of relatively earlier premature atrial beats to conduct to the bundle of His **(panels C** and **D).** The decrease in the A-V nodal effective refractory period after administration of atropine is accompanied by achievement of longer A-H intervals **(panels C** and **D).** At critically long A-H intervals a sustained supraventricular tachycardia occurred **(panel D).** Note the low to high sequence of atrial activation (Ae) and the inverted P wave in lead II during supraventricular tachycardia. Ae = atrial echo beat.

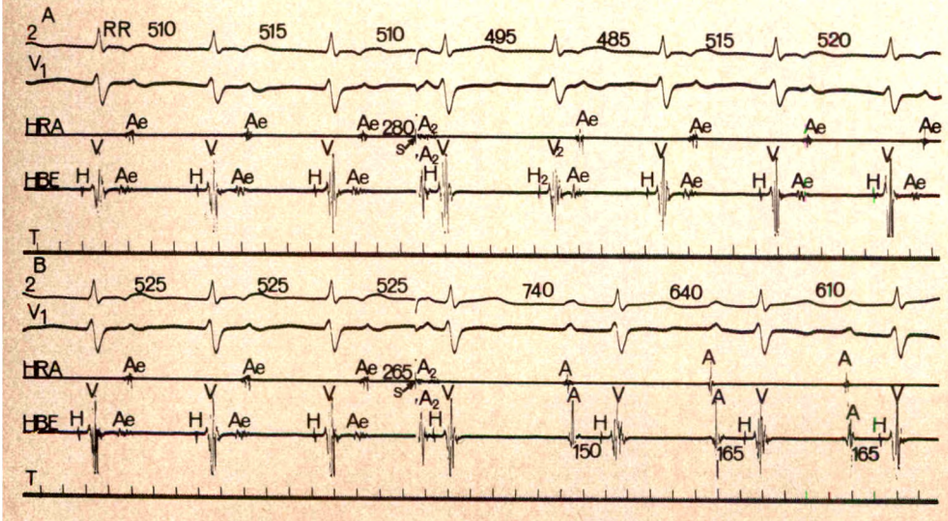

FIGURE 2. Case 1. Termination of supraventricular tachycardia. In **panel A,** a premature atrial beat is delivered at an Ae-A_2 interval of 280 msec and does not terminate the tachycardia. At a closer coupling interval of 265 msec **(panel B),** A_2 successfully terminates the tachycardia and sinus rhythm is restored.

induced A-V nodal Wenckebach cycles. After administration of atropine, sustained A-V nodal reentrant tachycardia regularly occurred at similar or shorter A-H intervals produced either by premature atrial depolarizations or by pacing-induced A-V nodal Wenckebach cycles.

Case 3 (Fig. 4): During control studies in this patient, A-V nodal reentry, as manifested by single or two consecutive atrial echo beats, could easily be elicited, but sustained A-V nodal reentrant tachycardia never occurred. After administration of atropine, sustained reentrant tachycardia was regularly initiated at the same A-H intervals that produced only one or two echo beats in the control period.

Cases 4 and 5: A-V nodal Wenckebach cycles induced by atrial pacing after administration of atropine resulted in sustained supraventricular tachycardia at the same period of A-V nodal conduction delay (A-H interval) that gave rise to only single atrial echo beats during the control period (Table II). The critical A-H intervals necessary for demonstration of A-V nodal reentry, although obtained with rapid atrial pacing, could not be attained during atrial premature coupling in these two patients.

Discussion

Mechanism of reentrant phenomenon in each case: It has been well established that A-V nodal reentry in the form of atrial echo beats requires a critical range of antegrade A-V nodal delay, most often elicited by premature atrial stimulation. Within the context of our present limited understanding of the reentrant phenomenon it is postulated that a requisite antegrade delay is necessary to allow recovery of the retrograde limb of the reentrant circuit, which may lead to reexcitation of the atrium. Within the limits of this currently accepted concept the following explanations are offered for the results obtained in these cases.

In Case 1, a prolonged effective refractory period of the A-V node prevented closely coupled atrial premature beats from being conducted with sufficiently long antegrade A-V nodal conduction time (A-H intervals) to permit recovery of the retrograde limb. This situation was reversed by atropine, which decreased the effective refractory period of the A-V node so that more closely coupled atrial premature beats could be conducted. These beats were associated with critically long A-H intervals and the necessary balance between conduction and refractoriness within the limbs of the reentrant circuit was achieved.

In Cases 3 to 5, most often only single and occasionally two consecutive atrial echo beats were elicited in the control period within a critical zone of

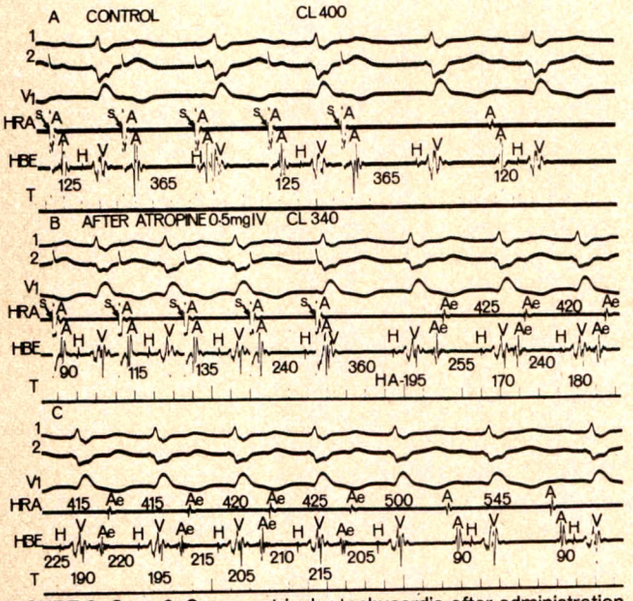

FIGURE 3. Case 2. Supraventricular tachycardia after administration of atropine. **Panel A** shows 3:2 A-V nodal Wenckebach cycles at a paced atrial cycle length of 400 msec. The A-H intervals of the first and second conducted beats measure 125 and 365 msec, respectively, and the third atrial beat blocks in the A-V node. The atrial stimulus is omitted after the last conducted beat of the second Wenckebach cycle following which a sinus escape beat occurs. After administration of atropine A-V nodal conduction of the Wenckebach type occurred at a paced atrial cycle length of 340 msec (**panel B**). The last (fifth) atrial paced beat conducts with an A-H interval of 360 msec and is followed by a sustained A-V nodal reentry. This figure also demonstrates spontaneous termination of supraventricular tachycardia. From the onset of the tachycardia there is a progressive decrease in the Ae-H interval (**panels B** and **C** are continuous) from 255 msec to 205 msec. There is a corresponding increase in the H-Ae interval and a final block of the impulse in the retrograde limb of the reentry circuit, and sinus rhythm ensues.

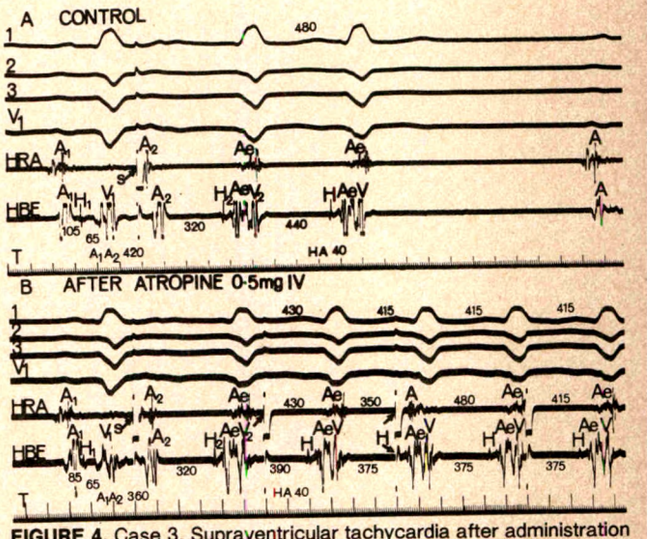

FIGURE 4. Case 3. Supraventricular tachycardia after administration of atropine. In **panel A** a premature atrial beat (A_2) is coupled to the preceding sinus beat at an A_1-A_2 interval of 420 msec. A_2 conducts with an A_2-H_2 interval of 320 msec and initiates unsustained A-V nodal reentry. The reentrant impulse conducts in antegrade fashion to the bundle of His with an Ae-H interval of 440 msec, then conducts back to the atrium and finally blocks in the antegrade limb. The H-Ae interval for the two reentrant beats is constant at 40 msec. After administration of atropine **(panel B)** sustained A-V nodal reentry is initiated at a similar degree of A-V nodal delay (A_2-H_2 interval 320 msec) as in the control period. After an initial variation, the Ae-H interval stabilizes at 375 msec. The H-Ae interval remains unchanged at 40 msec. Subsequent atrial stimuli **(panel B)** are for the most part ineffective and were delivered inadvertently. The third stimulus captures the high right atrium and results in fusion activation of the right atrium (low atrial electrogram; that is, Ae occurs at the expected time) (A-Ae interval 480 msec). This has no effect on the supraventricular tachycardia.

A-H delay. Failure of the atrial echo beats to conduct to the His-Purkinje system suggests that the antegrade limb of the A-V nodal reentrant pathway was refractory to the reciprocating impulse and therefore sustained reentry did not occur. The occurrence of sustained reentry after administration of atropine, which was initiated at levels of A-H delay comparable to those of the control period, implies that atropine decreased refractoriness of the antegrade limb to a degree that permitted continuous reciprocation. A decrease in A-V nodal refractoriness is a well known effect of the drug. Whether the retrograde limb was equally or unequally affected by atropine can only be conjectured. However, atropine did bring about the necessary balance between conduction and refractoriness within the reentrant circuit.

In Case 2, sustained supraventricular tachycardia occurred after administration of atropine at A-H intervals significantly shorter than those that in the control period resulted in either single or no atrial echo beats. Since sufficient antegrade A-V nodal delay (that is, longer A-H intervals) was achieved during the control period, it appears that improved conduction and shortening of refractoriness of only the crossover or retrograde pathway, or both, after administration of atropine were responsible for creating the balance necessary for the occurrence of sustained reentry. This possibility is also suggested by the mechanism of spontaneous termination of supraventricular tachycardia (Fig. 3). The initiation of sustained reentry at shorter A-H intervals after administration of atropine further attests to the importance of a balance between conduction and refractoriness in the limbs of a reentrant circuit.

Atropine and reentry: The possibility that atropine caused sustained reentry by changing atrial refractoriness can be summarily dismissed for the following reasons:

1. Small doses of atropine, as used in this study, produced no significant changes in atrial refractoriness as tested by the extrastimulus method.[11] After administration of atropine the effective refractory period of the atrium increased by 10 msec in Cases 1 and 3, decreased by 10 msec in Cases 2 and 5 and did not change in Case 4.

2. In four of five cases (Cases 2 to 5) atrial echo beats did occur in the control period and in Cases 3 to 5 the atrial echo beats were not followed by His bundle potentials, thus suggesting that the A-V node, not the atria, was refractory.

Although administration of small doses of atropine resulted in sustained A-V nodal reentry in these 5 patients, findings were not similar in the other 17 patients[11,12] who received the same amount of drug. There are several possible explanations for these differences: (1) Only 5 patients had the potential for development of reentrant supraventricular tachycardia that was unmasked by atropine; (2) in the other 17 patients the dose of atropine was either too small or too large; or (3) atropine simply did not produce the necessary balance of conduction and refractoriness between the antegrade and retrograde limbs of the reentrant circuit in these 17 patients.

Clinical implications: The results of this study help to elucidate some underlying mechanisms responsible for the success of therapeutic agents, such as digitalis and propranolol, in the management of patients with supraventricular tachycardia. Both digitalis and propranolol are known to prolong refractoriness of the A-V node and therefore may totally abolish manifestations of A-V nodal reentry.[17–19] These changes could result from prolongation of A-V nodal conduction and refractoriness in one or more sites in the reentrant circuit—the antegrade or retrograde limbs or crossover tracts—so that the premature atrial beats fail to induce the echo response. In some patients single or multiple atrial echo beats may still be demonstrable after administration of these drugs although sustained A-V nodal reentry may not occur if the necessary balance between conduction and refractoriness within the various limbs of the reentrant circuit is sufficiently altered by the therapeutic agents. Finally it must be pointed out that at times, these and other drugs may show what appear to be paradoxical effects on the reentrant phenomenon. We have observed in some patients A-V nodal reentrant atrial echo beats occurring only after administration of digitalis or propranolol whereas none were seen during the control period (unpublished observations). Likewise, it is conceivable that atropine may prevent sustained reentry in some patients with supraventricular tachycardia by altering the critical balance of conduction and refractoriness within the A-V node.

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Quantitative Study of the Supernormal Phase of Ventricular Excitability in Man

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The supernormal phase of excitability of the human heart was studied by means of fixed rate endocardial pacing in 11 patients with acute and chronic bradyarrhythmias. Ten of the eleven patients manifested a supernormal phase. The duration of the phase increased with increasing intensity of subthreshold stimuli and ranged from 91 to 148 percent of the Q-T interval. Subthreshold stimuli of a wide range of intensity could elicit a full response. Two types of supernormal phase, early and late in relation to the cardiac cycle, were observed. The latter was attributed to the summation of subthreshold stimuli with either spontaneous phase 4 depolarization of a ventricular ectopic pacemaker or atrial depolarization potentials. Its possible connection with Wedensky facilitation was suggested. The ventricle was less excitable after an ectopic beat than after a normally conducted beat.

Since Adrian[1] introduced the term supernormal excitation to denote a particular type of ventricular response to a subthreshold stimulus, the occurrence of this response in the mammalian[2–4] and human[3–10] heart has been repeatedly discussed. Nevertheless, few quantitative studies of the phenomenon have been performed and little is known about its mechanism. This study was designed to define quantitatively a supernormal phase of excitability in the human heart in terms of intensity of the effective subthreshold stimuli required to evoke it and its temporal relation to the cardiac cycle. The physiologic implications of the phenomenon and its bearing on Wedensky facilitation are also discussed.

Material and Methods

Eleven patients requiring temporary transvenous pacing for acute and chronic bradyarrhythmias were studied (Table I). Fixed rate endocardial pacing was performed in each case using a bipolar electrode catheter positioned at the apex of the right ventricle (Medtronic 5880A demand pacemaker and 5821 bipolar electrode catheter for endocardial pacing). This method enabled the pacemaker stimuli to fall at various portions of the cardiac cycle. After the diastolic threshold was determined, pacing was attempted with subthreshold stimuli at various levels of current intensity. A decrement of less than 0.1 milliampere between two consecutive levels of current intensity could not be used because of the technical properties of our pulse generators. The duration of the period of supernormal excitability was expressed as percent of the Q-T interval or as the time interval in seconds after the onset of the Q wave. The effectiveness of subthreshold stimuli was expressed as a percent of all stimuli administered at a given time.

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TABLE I

Clinical and Electrocardiographic Data in 10 Patients with Supernormal Ventricular Excitability

Case no.	Age (yr) & Sex	Diagnosis	Threshold (ma)	Stimulating Current Intensity (ma)	Q-T Interval (sec)	Time Scatter of Supernormal Excitability (sec)	100% Zone (sec)	Remarks
1	42F	AVB	2.0	1.8	0.50	0.48-0.58	0.50-0.54	
2	78M	AVB	5.0	4.8	0.42	0.36-0.62	0.40-0.52	Summation with blocked P
3	69F	AVB	2.0	1.7-1.9	0.44	0.40-0.94	0.42-0.48	
4	46M	AVB	2.0	1.9	0.40	0.34-0.50	0.40-0.42	Summation with phase 4 depolarization
5	66M	SSS	1.2	0.9-1.0	0.36	0.34-0.56	0.36-0.56	
6	61F	AMI	2.1	2.0	0.40	0.36-0.68	0.38-0.58	
7	69M	AVB	2.5	2.3	0.44	0.40-0.70		
8	58F	AMI	4.0	0.8-3.8	0.40	0.34-0.60	0.36-0.56	Summation with conducted P
9	68M	AVB	2.5	2.4	0.52	0.50-0.66	0.56-0.60	
10	73M	AMI	3.2	2.5-3.1	0.40	0.38-0.46	0.42-0.44	Summation with conducted P

AMI = acute myocardial infarction; AVB = chronic A-V block; P = atrial depolarization; phase 4 = spontaneous diastolic depolarization in the ventricle; SSS = sick sinus syndrome.

TABLE II

Influence of Variations in Subthreshold Current Output on the Duration of a Supernormal Period (SNP)

Case no.	Threshold Current (ma)	Effective Subthreshold Current (ma)	Time Scatter of Effective Impulse (sec)	Duration of SNP (sec)
3	2.0	1.9	0.40-0.92	0.52
		1.8	0.42-0.60	0.18
		1.7	0.42-0.48	0.06
5	1.2	1.0	0.34-0.56	0.22
		0.9	0.36-0.50	0.14
8	4.0	3.8	0.34-0.62	0.28
		3.5	0.34-0.60	0.26
		3.0	0.34-0.56	0.22
		2.5	0.34-0.50	0.16
		2.0	0.36-0.44	0.08
		1.5	0.36-0.44	0.08
		1.0	0.40	
10	3.2	3.1	0.38-0.46	0.08
		3.0	0.40-0.46	0.06
		2.9	0.42-0.46	0.04
		2.8	0.42-0.44	0.02
		2.6	0.42	

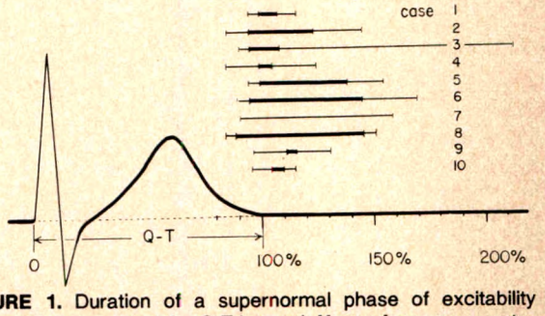

FIGURE 1. Duration of a supernormal phase of excitability expressed as percent of the Q-T interval. **Heavy bars** represent zones in which every subthreshold stimulus could produce an effective ventricular response.

Results

A supernormal phase of excitability was found in 10 of 11 patients studied (Table I).

Duration of the supernormal phase of excitability: A supernormal phase was observed not only at the end of the T wave but also at various points well after the T wave (Fig. 1, Table I). In five cases the supernormal phase measured 150 percent of the Q-T interval and in one case (Case 3) 91 to 213 percent of the Q-T interval.

In four cases a study of the duration of this supernormality at different current levels of subthreshold stimuli (Table II) revealed that the duration depended on the intensity of the subthreshold stimuli: Stronger subthreshold stimuli produced a longer supernormal phase. For example, in Case 8 (Fig. 2 and 3), the duration of the supernormal phase was 0.25, 0.16 and 0.08 second at respective current levels of 3.5, 2.5 and 1.5 ma. The lowest effective current of 1.0 ma could elicit a ventricular response only 0.40 second after the Q wave. In each case stronger stimuli extended the supernormal phase further into the late than into the early portion of diastole with an increment in the latter of up to 0.04 second.

Relative effectiveness of subthreshold stimuli: A subthreshold stimulus that could produce a full response in the midportion of the supernormal phase sometimes failed to do so near the beginning and end of the phase. The zone of 100 percent effectiveness usually occurred during a period constituting 100 to 125 percent of the Q-T interval (Fig. 1, Table I).

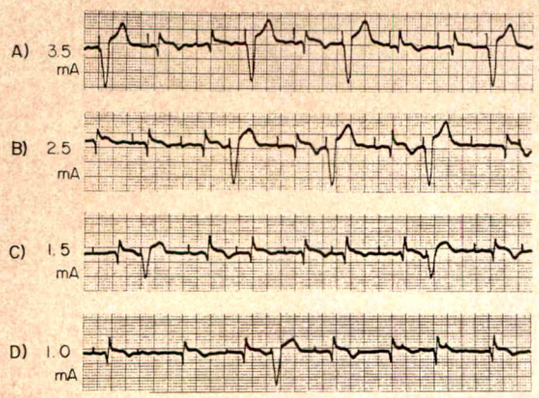

FIGURE 2. Case 8. The ventricular response to various levels of current intensity of subthreshold stimuli. Note longer duration of supernormal phase with stronger subthreshold stimuli (**A** and **B**). mA = milliamperes.

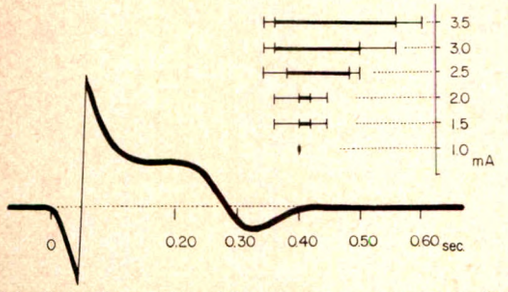

FIGURE 3. Case 8. Duration of the supernormal phase at different levels of subthreshold stimulus intensity. The duration increased with increasing strength of the stimuli. The horizontal axis represents time intervals after onset of the Q wave.

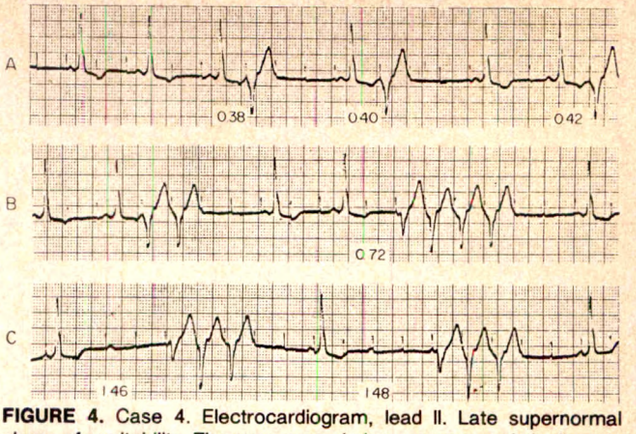

FIGURE 4. Case 4. Electrocardiogram, lead II. Late supernormal phase of excitability. The supernormal phase occurs early in diastole in **A**, both early and late in **B** and only late in **C**. Numbers at the bottom of each tracing represent time intervals after onset of the Q wave in seconds. Note that the two longer intervals in **C** (1.46 and 1.48 seconds) are approximately twice as long as the interval (0.72 second) in **B**.

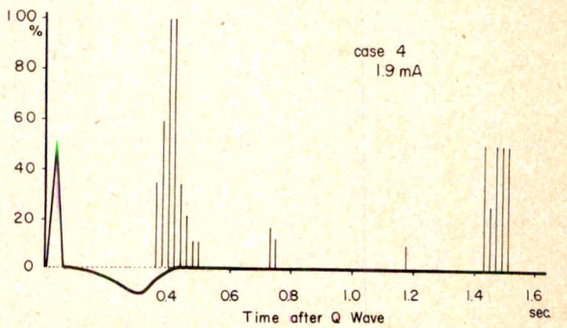

FIGURE 5. Case 4. Effectiveness of subthreshold stimuli at different time intervals after onset of the Q wave. Effectiveness is expressed in percent with reference to all the stimuli delivered at a given time interval in seconds after the Q wave.

Late supernormal phase: Unexpectedly, late occurrence of a supernormal phase was noted in five cases (Cases 2, 4, 6, 8 and 10). Figure 4 (Case 4) shows the occurrence of this late supernormal excitability in two ranges, namely, 0.72 to 0.76 second and 1.44 to 1.52 seconds after the Q wave. In each instance the first of the several consecutive supernormal responses differed in contour from the others. Figure 5 (Case 4) illustrates diagrammatically the frequency of late supernormal excitation at various points in the cardiac cycle. Figure 6 (Case 10) shows that an otherwise ineffective subthreshold stimulus could evoke and share ventricular depolarization with a sinus impulse giving rise to a beat analogous to a fusion beat only if the stimulus fell shortly after a P wave. A similar effect occurred with blocked atrial depolarization potentials in Case 2 (Fig. 7). However, in this case neither P waves nor subthreshold stimuli, occurring at the same time interval *after* the onset of spontaneous automatic beats, could by themselves produce a full response.

Supernormal phase after an ectopic beat: Figure 8 demonstrates in a case of atrial fibrillation the difference in ventricular excitability after a supraventricular and a ventricular ectopic beat. The subthreshold stimulus (ST 1) falling 0.44 second after an ectopic ventricular complex beat failed to elicit a response whereas the one after a conducted beat at the same time interval (ST 2) was able to do so. Although a similar phenomenon was noted in other cases in our study a quantitative analysis was not performed.

Discussion

Duration and location of supernormal phase: In contrast to our observations, the supernormal phase of excitability has been believed to take place within a fixed and narrow range of the cardiac cycle. Most previous studies performed in the human heart have defined the supernormal phase as a period in the cardiac cycle ranging between 80 and 120 percent of the Q-T interval,[4] for example, between the beginning of the downstroke of the T wave and the inscription of the U wave,[5] on the descending branch of the T wave,[9] or at the terminal portion of the T wave.[10] An experimental study[11] using a single fiber of isolated papillary muscle found supernormality of short duration at the end of phase 3 depolarization. By contrast, our results have demonstrated that the du-

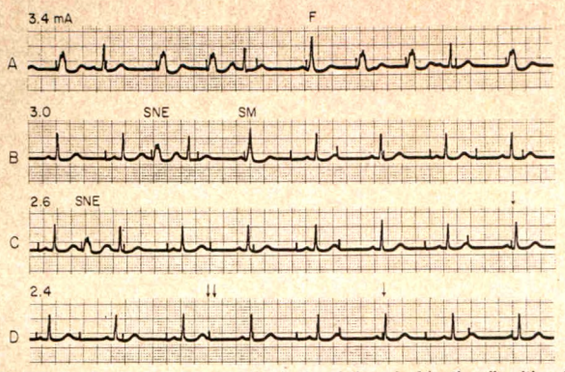

FIGURE 6. Case 10. Summation of subthreshold stimuli with atrial depolarization potentials. In **A,** a suprathreshold impulse precedes a normally conducted beat, giving rise to a fusion beat (F). Subthreshold stimulation is shown in **B** to **D.** SM = summation of a subthreshold stimulus with atrial depolarizing potentials. Note occasional failure of summation (↓) and absence of a supernormal phase of excitability (↓↓). SNE = supernormal phase of excitability.

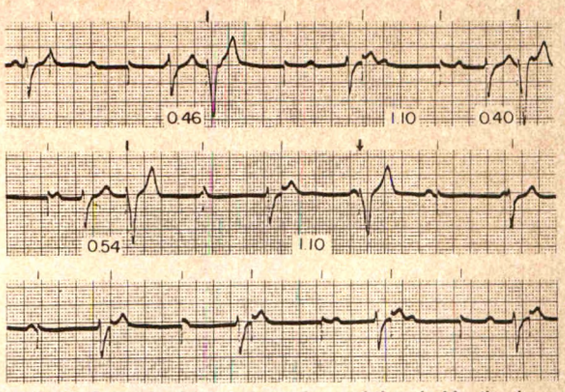

FIGURE 7. Case 2. Summation of a subthreshold stimulus with blocked atrial depolarization potentials in a case of complete A-V block. The **thick arrow** indicates summation, the **thick bars** an effective subthreshold stimulus and **thin bars** an ineffective stimulus. Figures at the bottom of each tracing represent time intervals of subthreshold stimuli from preceding spontaneous QRS complexes.

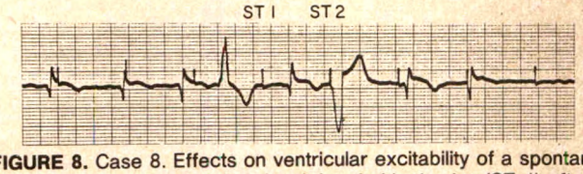

FIGURE 8. Case 8. Effects on ventricular excitability of a spontaneous ventricular ectopic beat. A subthreshold stimulus (ST 1) after a ventricular premature beat could not evoke a response in contrast to one (ST 2) occurring after a conducted beat (in atrial fibrillation).

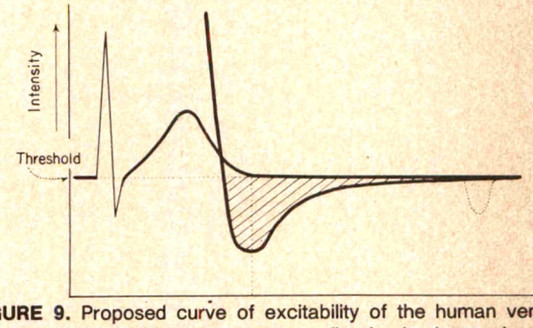

FIGURE 9. Proposed curve of excitability of the human ventricle. The lowest threshold (early supernormal) value is observed near the end of the T wave and is followed by a gradual rise until a plateau is reached. The **dotted area** denotes a late supernormal period due to summation of the subthreshold stimuli with a subsidiary phase 4 of spontaneous depolarization or with electrotonic spread of atrial impulses.

ration of the supernormal phase in the human ventricle is longer than hitherto believed and is dependent on the intensity of subthreshold stimuli (Fig. 2 and 3). A similar observation was made by Linenthal and Zoll,[6] who described a case in which the supernormal period lasted 0.04 and 0.1 second for stimuli of 2+ and 3+ intensity, respectively. This dependence of supernormal excitation on current intensity led us to believe that ventricular excitability was not uniform throughout diastole. The ventricle was very excitable during the period corresponding to the end of the T wave, becoming less so during the subsequent several hundred milliseconds until a diastolic threshold level was attained. (Fig. 9).

Occasionally, otherwise effective subthreshold stimuli failed to elicit a full response especially when they were given early or late in the supernormal period. The electrophysiologic interpretation of this finding could be as follows: During the supernormal phase, especially at its beginning and end, the depolarizing process must be taking place with such low margins of safety that even a small change in cellular environment may affect the sodium transport system, resulting in a temporary depression of excitability.

Enhancing of ventricular excitability by summation: In four cases, as described, the supernormal phase occurred unexpectedly late in diastole. Two characteristics of this finding are worth special mention: (1) The first beat due to late supernormal excitation differed from succeeding beats in contour, and (2) the second period of a late supernormal phase occurred at an interval after the Q wave measuring approximately twice the interval of the first period. These phenomena could be interpreted on the basis of summation of two impulses, one being the otherwise ineffective subthreshold stimulus, the other the potentials from a subsidiary ventricular ectopic pacemaker in the process of spontaneous (phase 4) diastolic depolarization. This could evoke a full ventricular response but the first beat would differ in contour from subsequent beats because its depolarizing process would have begun with an already reduced resting membrane potential.

Wedensky facilitation: This enhancing effect on ventricular excitability by summation has been experimentally demonstrated by Bailey et al.,[12] who elicited full excitation by administering a subthreshold stimulus properly timed with regard to the slow upstroke of the subthreshold depolarization. They called this Wedensky facilitation. Cranefield and Hoffman[13] reported similar results using a microelec-

trode technique in isolated Purkinje tissue. In addition to this temporal relation, spatial closeness of the origins of the stimuli must be a critical factor since electrotonic spread of subthreshold stimuli cannot travel far because of decremental changes.

Another point of evidence in favor of the ability of summation of impulses to produce a full response was found in Case 10, in which an otherwise ineffective subthreshold stimulus elicited a response when it was given at the end of a P wave (Fig. 6). The intensity of the current required for this type of summation was greater than that for the excitation induced at the end of the T wave (Fig. 6C). Similar events occurred in Case 2 (Fig. 7) and Case 8, and Soloff and Fewell[5] reported a similar observation (their Fig. 2). Arbel et al.[14] also demonstrated in man and dog this enhancing effect of atrial depolarization and attributed it to summation of subthreshold stimuli with electrotonic spread of atrial depolarization potentials. Like these authors, we found that this summation could take place whether or not atrial depolarization potentials were conducted to the ventricles (Fig. 6 and 7).

Thus, we have demonstrated by means of endocardial stimulation of the human heart that a supernormal phase of excitability can occur late in diastole and that its duration is dependent on the intensity of subthreshold stimuli. The physiologic basis may be summation of subthreshold stimuli (Wedensky facilitation), but this hypothesis needs confirmation in further studies.

Acknowledgment

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Hereditary Progressive Atrioventricular Conduction Defect

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New data on genetics, including an extensive pedigree and certain aspects of natural history, have been compiled on Family S, which is characterized by a hereditary progressive atrioventricular (A-V) conduction defect. Concordance analysis of heart block in affected parents and their offspring suggests as a working hypothesis transmission of diathesis for the defect by means of a Mendelian autosomal dominant factor. Regression of the defect in several relatives, including reversion from first degree heart block to normal A-V conduction, defies explanation at this time. However, rapport established with the unusually large (1,067 members) and cooperative kindred will permit longitudinal evaluation of these findings.

Hereditary factors are etiologically significant in a variety of cardiovascular problems.[1–10] Their importance in conduction defects was first reported by Morquio[11] in 1901 when he described atrioventricular (A-V) conduction disturbances in five brothers. Two years later Osler[12] described a family whose members had a slow pulse rate and Stokes-Adams attacks. The first electrocardiographic confirmation of familial heart block was reported in 1932.[13,14] Since then, more than 25 families with cardiac conduction disturbances of various kinds have been described.[10]

This report provides new and extended data from a large kindred characterized by a high incidence rate of a specific pattern of A-V conduction defect. This defect typically covers the range of first, second and third degree heart block and constitutes a newly described disorder: hereditary progressive atrioventricular conduction defect.[10] We believe that this study represents the most complete published report of a kindred with a cardiac conduction defect and that the data provide an important contribution toward elucidation of the etiology of the disorder.

Material and Methods

The syndrome of familial A-V conduction defect has been described previously in an initial report[10] on the S kindred. Since then, the study has been extended significantly, facilitating more critical explorations concerning the origin and natural history of the conduction defect (Fig. 1).

The earliest progenitor (generation I), determined in our pedigree search, produced five offspring (generation II), each of whom initiated one subdivision of the S kindred. One subdivision, in turn, produced 13 offspring (generation III), each of whom initiated a separate branch of the subdivision of the kindred. All our examinations have thus far been confined to members of one subdivision (that is, offspring of one person in generation II) composed of 13 branches (each starting in generation III) containing 1,067 persons.

A total of 12 field visits have been made to several midwestern and far western states where specific aggregations of the kindred reside. These field visits have been made with a cardiologist and various paramedical assistants

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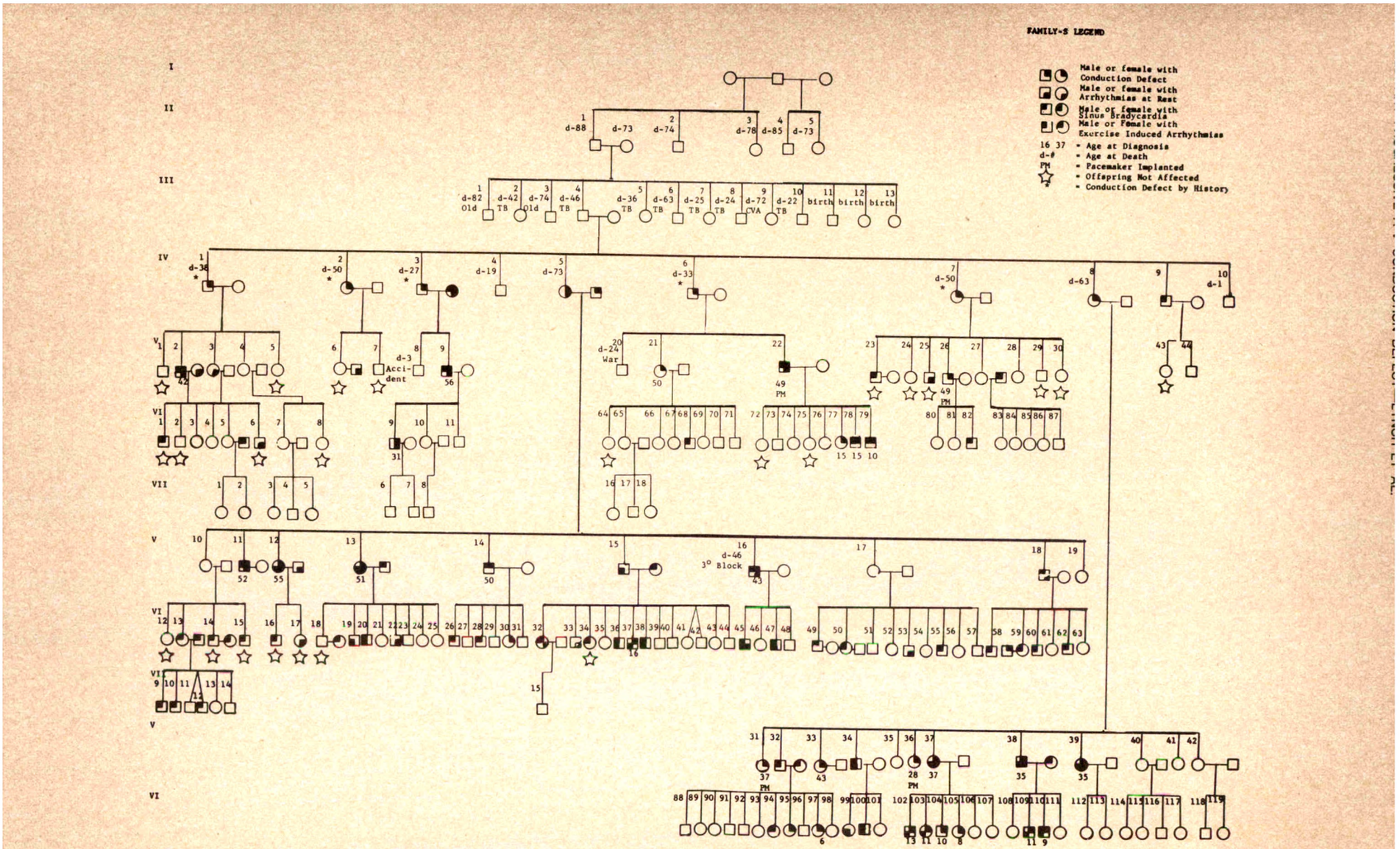

FIGURE 1. Pedigree of Family S showing hereditary progressive atrioventricular conduction defect transmitted through five generations.

who have worked closely with the family for several years, establishing excellent rapport and acquiring detailed familiarity with the family's geneology and medical problems. The help of family physicians has been enlisted so that detailed medical information is constantly made available to the research team. In addition, hospital records have been secured as well as pathologic confirmation of all major disorders including cardiovascular diseases.

We have examined the members of three branches in one subdivision. The examined members in two of these branches have shown no evidence of cardiac disorders. Members of the third branch, studied extensively, manifested a conduction defect.

An extensive pedigree of this kindred has been constructed (Fig. 1). The pedigree is designed to facilitate evaluation of (1) conduction defects, (2) sinus bradycardia, (3) cardiac arrhythmias at rest, and (4) the occurrence of exercise-induced cardiac arrhythmias. As originally reported,[10] the electrocardiographic abnormalities in family S include the following:

"(1) a progressive increase in atrioventricular conduction delay culminating in a complete heart block, (2) QRS complex normal in configuation and duration, (3) a normal QT interval, (4) a poor progression of R wave across the right precordium, (5) no evidence of intraventricular conduction defects, (6) no evidence of any cardiac chamber enlargement, (7) rare atrial and ventricular arrhythmias, only late complications, and (8) progression from first degree to complete heart block usually gradual but occasionally fulminant leading to sudden death within two to three years." [10]

Exercise-induced arrhythmias were defined as documented atrial and ventricular arrhythmias occurring during graded exercise tests. Arrhythmias at rest were defined as arrhythmias occurring in the resting state accompanied by electrocardiographic evidence of atrial or ventricular ectopic activity, or both. Sinus bradycardia (rate less than 60 beats/min) was documented by electrocardiogram.

The occurrence of heart block in the S kindred was subjected to concordance analysis, and the results are listed in Tables I to III.

Results

The S kindred includes five major subdivisions. The first subdivision consists of 13 branches totaling 1,067 members. To date, all examinations have been conducted in only three of these branches. Members of two of the branches have not displayed symptoms of the cardiac disease. One branch consists of 10 families comprising 378 persons of whom 44 died prior to our study. Electrocardiograms have been recorded in 255 of the 334 members (76 percent) of that branch who are still living. Among these 255 members, 87 (34 percent) have an arrhythmia at rest, including sinus bradycardia, and 40 (16 percent) have a conduction defect as determined by electrocardiogram or by reliable history.

We have documented findings of regression as well as progression of the conduction defect in this disorder. Specifically, one male subject (aged 18 years) had definite second degree heart block at one time and, 1 year later, his condition had reverted to first degree heart block. In three children (two 11 year old boys and one 8 year old girl) first degree heart block reverted to normal A-V conduction. In addition, in an 11 year old boy oscillation between first degree heart block and normal A-V conduction has been observed for 4 years.

Results of chest X-ray examination and coronary angiograms, performed in the proband and her similarly affected sister, were normal.[10] In addition, no disorders known to be associated with abnormalities of the cardiac conduction system were found to occur in excess in members of kindred S.

TABLE I

Parents in the S Kindred with Heart Block and Their Offspring: Pair Concordance (C) and Discordance (D) for Heart Block

Affected Parent and Offspring Pairs	Pairs (no.)		
	C	D	Total
Mother-offspring	16	42	58
Mother-daughter	9	25	34
Mother-son	7	17	24
Father-offspring	11	34	45
Father-daughter	3	16	19
Father-son	8	18	26
Parent-offspring	27	76	103
Parent-daughter	12	41	53
Parent-son	15	35	50

TABLE II

Individuals in the S Kindred with Heart Block and Their Siblings: Pair Concordance and Discordance for Heart Block

	Affected Females			Affected Males		
	C	D	Total	C	D	Total
Siblings of affected females	35	35	70	19	26	45
Siblings of affected males	30	41	71	18	26	44

TABLE III

Kin of Affected Members of S Kindred and Their Empiric Risks for Heart Block

Kinship Category	Kin of Affected Females in the S Kindred		Kin of Affected Males in the S Kindred	
	no.	Empiric Risk	no.	Empiric Risk
Daughters	34	0.26	19	0.16
Sons	24	0.29	26	0.31
Sisters	70	0.50	71	0.42
Brothers	45	0.42	44	0.41

Heart Block, Concordance Analysis

Table I lists the number of observed concordant and discordant pairs in parents with heart block and their offspring in the S kindred. The risks for heart block in the offspring of affected mothers belonging to the S kindred are 0.40 for daughters and 0.29 for sons. These frequencies are not significantly different from each other. The observed risks for heart block

in the offspring of affected fathers are somewhat different from those observed in the offspring of affected mothers. The empiric risk for heart block in daughters of affected fathers is 0.16, and that for sons of affected fathers is 0.31. The risks differ according to sex of the offspring and sex of the affected parent, but the differences are not statistically significant.

Table II shows the distribution of concordance and discordance for heart block among affected members of the S kindred and their siblings, tabulated according to the sex of each affected member and the sex of each sibling. The empiric risks for heart block in siblings of affected members of the S kindred are as follows: for a female with an affected sister, 50 percent; for a female with an affected brother, 42 percent; for a male with an affected brother, 41 percent; and, for a male with an affected sister, 42 percent. There is no statistically significant difference associated with the sex of the sibling at familial risk or with the sex of that individual's affected sibling.

Table III shows the number of persons involved in each of the studied kinship categories, and the empiric risks for the daughters, sons, sisters and brothers of members of the S kindred with heart block.

Discussion

Various cardiovascular disorders have been observed to be familial and some have been associated with simple genetic modes of transmission in certain kindreds. In the broad field of congenital heart disease, the reported incidence of risk in the general population is typically 5 to 7 per 1,000 live births. When a family already has one affected child, however, the risk for subsequent offspring increases to 2 to 4 percent. When two or more siblings are affected, the risk for subsequent offspring of the same parents approaches 5 to 8 percent.[1] Finally, when the broad category of congenital heart disease is subdivided into specific categories, such as supravalvular aortic stenosis or the secundum variety of atrial septal defect, one encounters certain kindreds in which the defect is apparently transmitted by an autosomal dominant gene with variable penetrance.[2,3] Chromosomal disorders, such as the G_1-trisomy syndrome (associated with A-V defect or ventricular septal defect) or Turner's syndrome (associated with coarctation of the aorta or aortic valvular stenosis[4]), are frequently associated with congenital heart defects. The broad category of collagen vascular diseases,[5] such as Marfan's syndrome, Ehlers-Danlos syndrome and Hunter's and Hurler's syndromes, are associated with various congenital heart defects as well as disorders generally characterized as abiotrophies, such as dissecting aortic aneurysm (Erdheim's cystic medial necrosis). Other categories include associations of cardiac defects with hereditary neurologic[6] and primary muscular[7] disorders; and associations of skeletal defects with cardiovascular disease such as those occurring in the heart-limb disorders found in autosomal dominantly inherited Holt-Oram syndrome showing association between upper limb abnormalities and atrial septal defect.[8] Familial occurrence of coronary artery disease has also been reported.[9]

TABLE IV

Hereditary Cardiac Conduction Disturbances and Arrhythmias That Are Not Associated with Intracardiac Defects or Major Medical Disorders

Disturbance	Mode of Genetic Transmission
1. Heritable Q-T prolongation with deafness[15] (Jervell and Lange-Nielsen syndrome)	Autosomal recessive
2. Heritable Q-T prolongation without deafness[16]	Autosomal dominant
3. Possible progressive A-V block in a single family similar to S[17]	Autosomal dominant
4. Prolonged P-R interval (single family)[18]	Autosomal dominant
5. Intraventricular conduction defect and complete heart block[19]	Autosomal dominant
6. Familial bundle branch block[20]	Autosomal dominant
7. Familial atrial fibrillation[21,22]	Autosomal dominant and autosomal recessive
8. Familial sinus node disease[23]	Possible autosomal dominant
9. Familial heart block and sinus bradycardia[24]	Autosomal dominant
10. Familial pure sinus bradycardia[25]	Autosomal dominant
11. Wolff-Parkinson-White syndrome[26]	Autosomal dominant
12. Familial cardiac arrhythmia[27] (ectopic tachyarrhythmias)	Autosomal dominant

Hereditary cardiac conduction disturbances—modes of transmission: Since the initial report of familial conduction disturbance by Morquio,[11] investigators have described families with disorders involving the sinus node, atrioventricular conduction and the bundle of His and its branches. In general, the clinicopathologic features of these conditions in families have been specific. Genetic heterogeneity has frequently been encountered. Table IV lists cardiac conduction disturbances that have been reported to be genetically transmitted, either as specific entities or as components of syndromes.

A trait or character that can be dichotomized (for example, "affected" versus "not affected") may be subjected to comparisons of concordance rates observed in different pair categories. Such comparisons, by themselves, may not prove transmission according to a particular hypothesized genetic mode, but they can be utilized to determine whether the data reveal sex limitation, sex influence or sex linkage in transmission or manifestation of a trait. Concordance comparisons may also indicate whether the observations are consistent with a particular hypothesized mode of genetic transmission. The concordance rate between pairs of affected parents and their offspring, for a trait associated with a single autosomal gene not showing sex influence, equals the product of the probability for transmitting the gene to each off-

spring and the gene's penetrance. Accordingly, the data tabulated in Tables I to III are consistent with concepts that involve no sex influence or sex limitation in transmission or manifestation, and vertical transmission from parent to offspring. We suggest a Mendelian autosomal dominant mode of transmission of diathesis to the conduction defect, with reduced penetrance and somewhat variable expressivity, as a working hypothesis of the etiology of the syndrome in this remarkable kindred. This working hypothesis is consistent with the data showing empiric risks ranging from 0.16 to 0.50 (Table III), but the possibility of additional etiologic factors cannot be excluded.

Comprehension of the natural history of the disorder will require more investigation. The instances of regression of the defect, such as reversion from first degree heart block to normal A-V conduction in three of the children, cannot be explained at this time.

Pathogenesis: The pathogenesis of this syndrome is unknown. Atherosclerosis, particularly of the coronary arteries, was not a striking finding in the two affected patients who underwent coronary arteriography.[10] The heart (autopsy specimen) of one patient who died from this syndrome was examined by us. Unfortunately, because this patient died in an area remote from our medical center and we had not established prior communication with the pathologist who performed the autopsy, special studies of cardiac tissue were not performed. When we received the specimen the right atrium was not present. However, in the remainder of the heart there was no evidence of significant coronary arterial atherosclerosis, heart muscle disease, valvular heart disease or infiltrative diseases. No clues could be obtained on the pathologic features contributory to this patient's sudden death, save that of clinical knowledge that he had a history of complete heart block. Cardiac biopsy specimens obtained from two sisters in Family S who underwent transthoracic pacemaker implantation showed no evidence of a disease process.

Concluding Remarks

The observed rates of pair concordance for heart block between affected parents in the S kindred and their offspring and the empiric risks for such manifestations showed small but not statistically significant differences (0.16 to 0.31) associated with the sex of the affected parent and the sex of the offspring. Smaller sex-related differences were observed in sibling pair concordance rates, which ranged from 0.41 to 0.50. A tentative working hypothesis has been suggested, involving transmission of the diathesis for the disorder by means of a Mendelian autosomal dominant factor. The sex-related differences among the several parent-offspring concordance rates, the smaller sex-related differences among the several sibling-pair concordance rates, and the difference between the parent-offspring and sibling-pair categories limit full acceptance of this hypothesis, but do not negate it.

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Abnormalities of Left Ventricular Function and Geometry in Adults with an Atrial Septal Defect

Ventriculographic, Hemodynamic and Echocardiographic Studies

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Left ventricular function and motion in 12 adults with an ostium secundum atrial septal defect were analyzed utilizing biplane cineangiography. Values for left ventricular end-diastolic volume index, stroke volume index, ejection fraction, left ventricular end-diastolic pressure and mean rate of circumferential fiber shortening were compared with values in an age-matched group of 11 normal subjects. Comparisons of ventriculographic and echocardiographic data were also made in 5 patients and 10 control subjects. Cardiac index was smaller in patients than in the normal subjects (3.6 vs. 4.5 liters/min per m^2, $P < 0.01$). Although left ventricular end-diastolic pressure was similar (8 mm Hg in both groups), the end-diastolic volume index was significantly smaller in patients than in normal subjects (56 vs. 76 ml/m^2, $P < 0.05$). Stroke volume index was also significantly smaller in patients (40 vs. 52 ml/m^2, $P < 0.01$). The two groups had similar values for ejection fraction (65 ± 2 percent [standard error of the mean] in patients vs. 68 ± 2 percent in normal subjects), circumferential fiber shortening velocity (1.67 ± 0.13 vs. 1.81 ± 0.15 circumferences/sec), heart rate (91 ± 7 vs. 90 ± 5 beats/min) and mean systemic arterial pressure (92 ± 5 vs. 87 ± 3 mm Hg). Early systolic bulging of the upper ventricular septum toward the right ventricle was seen in 10 of 12 patients with an atrial septal defect but in no normal subject. Echocardiographic data supported these findings. No other abnormalities of motion were consistently noted. It is concluded that the left ventricle of patients with an atrial septal defect is subnormal in volume and abnormal in sequence of contraction of the septum and is characterized by apparent decreased distensibility.

Many investigators[1–10] have concluded that dysfunction of the left ventricle may play a role in the pathophysiology of atrial septal defect. Although it is considered to figure prominently in the congestive heart failure that limits both life expectancy[6–8] and operative results,[8,9] the mechanism for this effect remains unknown. Cineventriculography has not been utilized previously in a systematic manner to investigate the function of the left ventricle in patients with an atrial septal defect. In this study we emphasize ventriculographic and echocardiographic methods to gain further insight into this question.

Methods

Twelve adult patients with an ostium secundum atrial septal defect and without signs of cardiac failure were studied by cardiac catheterization while at rest. Selective or nonselective coronary angiography, performed in 11 of these patients, revealed normal coronary arteries. Data in these patients were compared with similarly obtained data in a group of 11 age-matched control

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TABLE I

Clinical and Hemodynamic Characteristics

Case no.	Age (Yr) & Sex	Pressures (mm Hg) RAm	LAm	Right Ventricle S	Right Ventricle ED	Left Ventricle S	Left Ventricle ED	Pulmonary Artery S	Pulmonary Artery D	Aorta S	Aorta D	Qp/Qs
Patients with Atrial Septal Defect												
1	40M	4	4	28	4	120	5	20	5	120	72	3:1
2	41M	3	5	55	6	145	12	55	20	145	75	3:1
3	49F	8	8	48	8	140	8	48	14	135	70	2.7:1
4	39F	2	2	20	4	110	10	20	4	100	64	2.4:1
5	57F	10	10	90	20	160	10	90	35	160	100	1:1
6	20M	4	4	35	8	—	7	21	4	138	78	1.8:1
7	40F	1	2	20	6	105	4	24	4	105	55	1.4:1
8	18F	6	3	37	6	126	8	27	10	126	70	3:1
9	45F	0	2	18	0	90	6	16	4	95	50	3:1
10	50F	4	7	32	10	100	6	24	10	150	80	3.5:1
11	44F	1	1	20	5	120	3	20	8	110	60	2.4:1
12	29F	2	3	22	3	130	11	20	4	130	75	3.5:1
M ± SEM	43 ± 2	4 ± 0.9	5 ± 0.8	35 ± 6	7 ± 1.4	122 ± 6	8 ± 1	32 ± 6	10 ± 3	126 ± 6	71 ± 4	2.6:1
Control Subjects												
1	41M	3	6	20	4	110	8	20	8	110	60	
2	49F	1	10	28	0	80	10	24	12	80	50	
3	43F	1	—	16	0	135	10	16	2	135	75	
4	41M	4	—	20	4	115	4	22	12	130	80	
5	54M	2	—	18	0	137	12	18	4	137	74	
6	41M	10	10	36	12	120	10	32	16	120	90	
7	33M	2	—	24	0	100	8	22	8	100	60	
8	40M	2	—	20	2	110	6	18	8	110	60	
9	47F	1	—	30	5	118	5	18	4	118	70	
10	41M	0	—	20	7	107	4	20	9	107	78	
11	45M	—	—	—	—	125	8	16	4	125	70	
M ± SEM	39 ± 3	3 ± 0.9	8.6 ± 2.3	23 ± 2	3 ± 1.2	114 ± 5	8 ± 0.8	21 ± 1	8 ± 1	116 ± 5	68 ± 3	
P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	

D = diastolic; ED = end-diastolic; LAm = mean left atrial; NS = difference between two groups not significant; M = mean; *P* = probability; Qp/Qs = ratio of pulmonary to systemic flow; RAm = mean right atrial; S = systolic; SEM = standard error of the mean.

subjects who underwent cardiac catheterization for evaluation of a "chest pain syndrome" but were found to have no discernible cardiovascular disease.

All subjects had right and left heart catheterization with pressures recorded through a fluid-filled catheter system with an Electronics for Medicine oscillographic recorder. Pulmonary and systemic flow data were measured by the Fick oxygen method. Biplane cineangiography (30° right anterior oblique and 60° left anterior oblique projections) was performed using Siemens radiographic equipment at a filming rate of 100 frames/sec after the injection of contrast material, most often into the left ventricle but occasionally into the left atrium or pulmonary artery. Ventricular volume and mass were determined by a modification of the method of Dodge et al.[11] Premature ventricular contractions and the beats following them were excluded from analysis. Ejection fraction was defined as the ratio of stroke volume to end-diastolic volume, as determined by angiography. Percent shortening of the major and minor axes was measured in both the right anterior oblique and left anterior oblique views. Angiographic cardiac index was determined for the left ventricle. The mean rate of circumferential fiber shortening was measured using a modification of the method of Gorlin et al.[12] and Karliner et al.[13] The mean rate of circumferential fiber shortening was measured in both the right anterior oblique and left anterior oblique projections at both one half and one third the distance from the base to the apex.

The motion of the interventricular septum as determined with ventriculography was compared with the echocardiographic analysis of septal motion in 5 patients with an atrial septal defect and in 10 control subjects. Echocardiograms were obtained using a nonfocused transducer, 2.25 megahertz, 13 mm diameter, and a Unirad Series C ultrasonoscope with a Tektronix strip chart recorder.

Results

The clinical and hemodynamic characteristics of the two study groups are summarized in Table I. These groups were essentially age-matched. Female subjects predominated in the group with an ostium secundum atrial septal defect[7,14] and male subjects in the group with chest pain. No significant difference in pressures was noted between the two groups.

Left ventricular cardiac output and volumes: Figure 1 shows comparisons of angiographically determined cardiac index and its component parts, the angiographic stroke volume and simultaneously determined heart rate. The mean cardiac index in the group with atrial septal defect was significantly lower than in the normal group (3.6 vs. 4.5 liters/min per m^2, P <0.01). The heart rates were essentially the same. The patient group had a significantly lower value for stroke volume than the normal group (41 vs. 52 ml/m^2, P <0.01). These results were unaffected by data from two patients with an atrial septal defect who had sinus tachycardia and reduced stroke volume.

Figure 2 compares the angiographic volumes in the two groups. The mean end-diastolic volume index

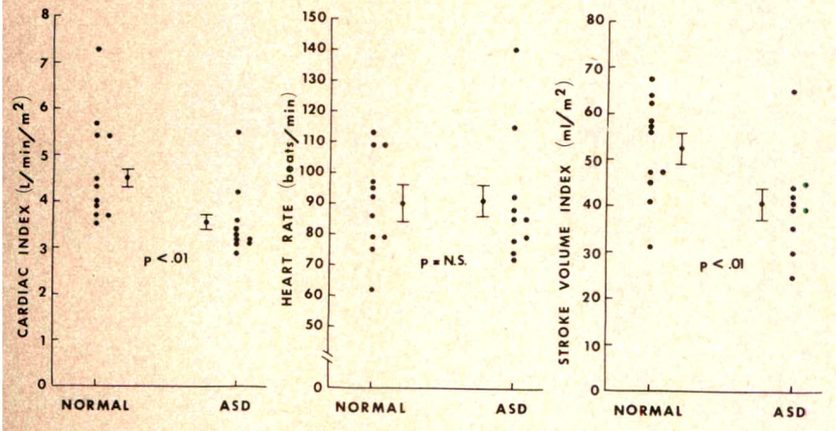

FIGURE 1. Comparisons of angiographically determined cardiac index, heart rate and stroke volume index in normal subjects and the 10 (of 12) patients with atrial septal defect (ASD) in whom quantitative calibration of the ventriculogram was available. N.S. = not significant; p = probability.

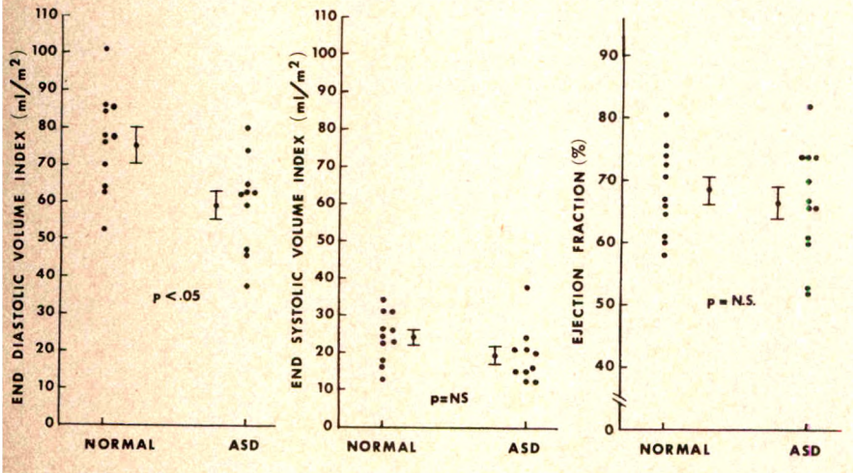

FIGURE 2. Angiographic end-diastolic and end-systolic volume indexes in normal subjects and in the 10 patients with atrial septal defect and calibrated ventriculograms. Ejection fractions were compared in all subjects in the series.

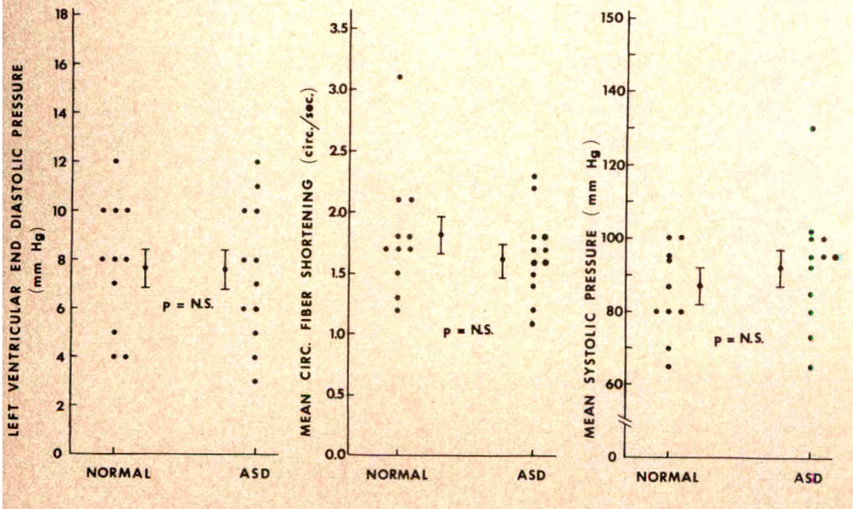

FIGURE 3. Left ventricular end-diastolic pressures, mean rate of circumferential (CIRC.) fiber shortening, and mean systolic systemic arterial pressures in normal subjects and patients with an atrial septal defect (ASD).

was significantly less in the patients with an atrial septal defect than in the normal subjects (59 vs. 75 ml/m^2, P <0.05). However, values for both end-systolic volume index and ejection fraction were similar.

Determinants of left ventricular volumes: There was no statistically significant difference between the two groups in left ventricular end-diastolic pressure, mean systolic arterial pressure or mean rate of normalized circumferential fiber shortening measured in either projection or either chord (see Methods) (Fig. 3).

Regional ventricular shortening: There was no significant difference in the degree of shortening of any axis except the major axis in the left anterior oblique view (Fig. 4).

Motion analysis of the interventricular septum: In all subjects, the first motion of the interventricular septum during systole was an anterior movement of its uppermost portion away from the posterior left ventricular wall (Fig. 5). This occurred within approximately 0.05 second of the initiation of systole. In the normal group, this was followed by uniform inward motion of all ventricular walls, including the septum, throughout the rest of the systole. However, in 10 of the 12 patients with an atrial septal defect, this initial anterior movement of the uppermost septum was followed not by inward contraction but rather by temporary akinesia while an area more distal to it began bulging anteriorly. This last abnormal motion was more pronounced in some patients than in others. In the last phases of systole, uniform inward contraction occurred in the group with atrial septal defect so that the end-systolic ventricle became similar in size and shape to that seen in the control group

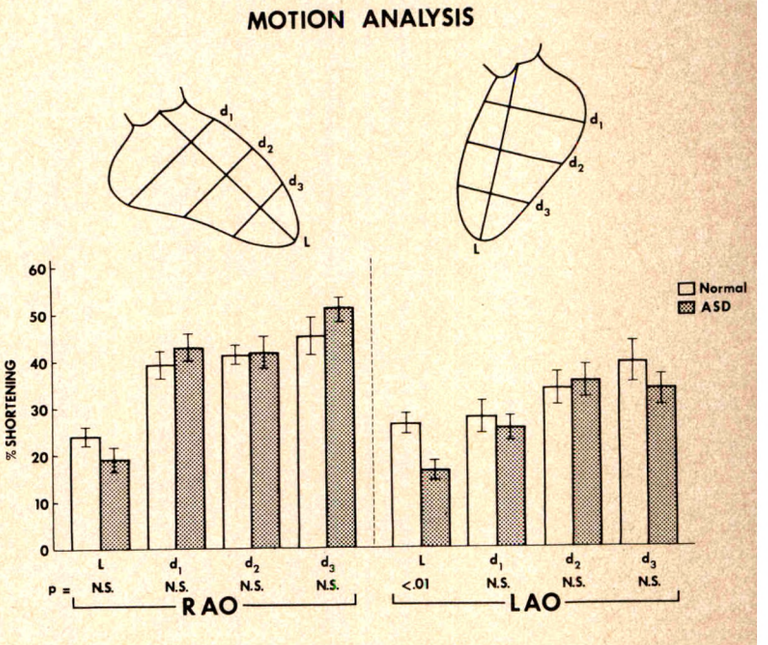

FIGURE 4. Comparison of the degree of shortening of all major and minor axes in both right anterior oblique (RAO) and left anterior oblique (LAO) projections in normal subjects and patients with an atrial septal defect (ASD). The ventricular silhouettes illustrate the particular chords being measured.

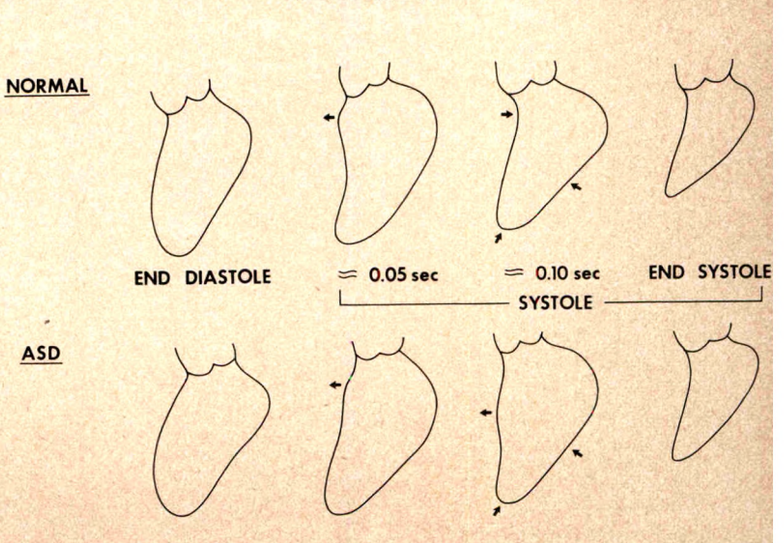

FIGURE 5. Representative outlines of the ventricle in the left anterior oblique view illustrating septal motion during systole for both normal subjects and patients with an atrial septal defect (ASD). **Arrows** indicate direction of movement of a particular area.

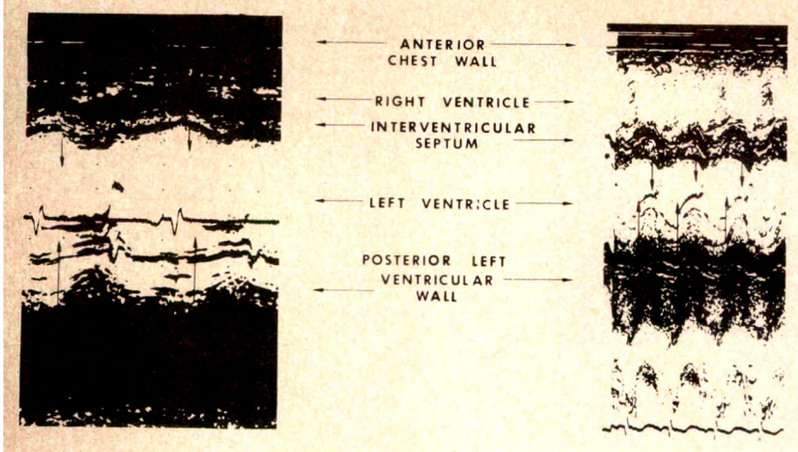

FIGURE 6. Representative echocardiograms from a normal subject and a patient with an atrial septal defect (ASD). **Arrows** indicate the initiation of movement of a particular surface. The recording speed used in the normal example is greater than that used in the echocardiogram from the patient with the septal defect. The latter example illustrates "reverberation."[27]

(Fig. 5). One of the two patients with an atrial septal defect who exhibited entirely normal septal motion had a balanced shunt and pulmonary hypertension.

Ventriculographic-echocardiographic correlations: Septal motion as analyzed with angiography was compared with septal motion determined with echocardiography (Fig. 6). All 11 control subjects had normal echocardiographic septal motion, with the ventricular septum beginning posterior movement nearly simultaneously with the initiation of anterior movement by the posterior left ventricular wall. All five of the patients with an atrial septal defect who had echocardiograms performed manifested abnormal septal motion, in that the septum did not begin movement simultaneously with the posterior wall. Figure 6 illustrates one of several variations (type A as well as type B of septal motion abnormality).[15–18] All five of these patients had the abnormal angiographic septal motion described. Neither of the two patients with an atrial septal defect and normal angiographic septal motion underwent echocardiography.

Discussion

Pathophysiology of atrial septal defect: In 1956 Dexter[1] explained the clinical manifestations of atrial septal defect in terms that have become the accepted pathophysiologic basis of the disorder. Summarizing not only his own earlier work but also that of several others,[19–22] he stated that when an atrial septal defect is large (more than 3 cm^2), pressures during diastole are essentially identical in both atria and in both ventricles. Second, although left ventricular stroke output remains essentially the same over wide ranges of left ventricular end-diastolic pressure, right ventricular stroke output can be large or small at any given level of right ventricular end-diastolic pressure. He interpreted this to mean that at high levels of end-diastolic pressure the left ventricle is malfunctioning since it does not increase its output pari passu. Thus, the failing left ventricle maintains a stable output only at the expense of elevation of its end-diastolic pressure. When right ventricular failure occurs, it results in a decreased stroke volume that leads to an increased residual volume. This increased right ventricular residual volume leads to reduced right ventricular compliance relative to left ventricular compliance. Since the direction of the shunted blood is determined not by a pressure gradient but rather by a difference in relative resistances to flow, right ventricular failure leads to a decreased left to right shunt and ultimately to right to left shunting and cyanosis. Left ventricular failure, on the other hand, leads to increased diastolic pressure and therefore to bilaterally increased atrial pressure and consequently to signs and symptoms of "right heart" congestive failure.

Dexter was unable to explain why the left ventricle should fail in these patients, who do not have increased left ventricular volume or pressure work. Some patients studied had conditions, including hypertension, mitral regurgitation and atrial fibrillation, that might be associated with left ventricular failure, but these were of mild degree and could not fully explain the failure. Tikoff et al.[5] substantiated Dexter's analysis and observed that the incidence of heart failure increased with age. Other investigators found evidence of left ventricular failure during postoperative evaluations but their findings were difficult to separate from the possible influences of operation. For example, Davies et al.[4] reported on seven patients studied because of persistence of symptoms postoperatively; all had elevation of pulmonary capillary wedge or left ventricular end-diastolic pressure, or both.

Tikoff et al.[2] described 13 patients with atrial septal defect who had preoperative heart failure as defined by clinical signs or the presence of a right atrial pressure greater than 8 mm Hg and, thus, bilaterally increased atrial pressure. When these patients were studied 5 months to 10 years after operation, only

one had completely normal hemodynamic findings and only four had marked reduction of symptoms after septal closure.

Left ventricular dysfunction in atrial septal defect: From these studies, one might conclude that some patients with an atrial septal defect have damage to the left ventricle that may persist after closure of the defect and cause symptoms. One still does not know the etiology of the process or how commonly it occurs in any total population of patients with atrial septal defect.

Epstein et al.[23] recently described 12 asymptomatic adult patients who had an atrial septal defect closed surgically. These patients were studied 6 to 15 months postoperatively while performing upright exercise. Although hemodynamic values were essentially normal at rest, during intense upright exercise 7 of the 12 patients had a lower cardiac index than a group of age-matched control subjects (6.6 vs. 8.9 liters/min per m^2). In these patients heart rate, but not stroke volume, was increased appropriately. Their report suggests that left ventricular dysfunction may be present subclinically after operation even in asymptomatic patients. However, since the study was performed postoperatively, it is not helpful in defining the etiology of the dysfunction.

On the other hand, Flamm et al.[10] studied a group of 25 adults with an atrial septal defect before operation both at rest and upon exercise. Ten of these patients had clinical evidence of congestive heart failure at rest and another seven had evidence of dysfunction of the right or left ventricle, or both, with exercise. Left ventricular function was considered abnormal if the following were present: (1) left ventricular end-diastolic pressure greater than 16 mm Hg at rest or during exercise, (2) an increase during exercise in systemic cardiac output by less than 550 ml/min for each 100 ml/min increase in oxygen consumption, or (3) a decrease in left ventricular stroke volume from rest to exercise associated with an increase in left ventricular end-diastolic pressure. Right ventricular function was considered abnormal if the right ventricular stroke volume decreased from rest to exercise in association with an increase in right ventricular end-diastolic pressure. On the basis of these definitions, Flamm et al. found no instances of left ventricular failure unassociated with right ventricular failure. Further, there were eight instances of normal function of both ventricles. They concluded that the left ventricle of these adult patients with an atrial septal defect was generally normal before operation and failed only as a result of right ventricular failure.

Manifestations and cause of left ventricular dysfunction: In our studies of adults with various sizes of atrial septal defect we have shown evidence that the left ventricle is not entirely normal in its performance or in its morphologic characteristics. These patients are characterized by a presumably chronically low systemic cardiac index due to a decrease in stroke volume rather than in heart rate (as also found by Epstein et al.[23]). The decreased stroke volume is due to a decreased end-diastolic volume with a normal ejection fraction. Attempts to define further this apparent disorder of cardiac autoregulation have yielded evidence of (1) normal afterload (systemic arterial pressure), (2) unchanged contractility during ejection (mean rate of circumferential fiber shortening and ejection fraction), and (3) normal heart rate.

The only abnormality among the indexes of contractility that we measured was the degree of shortening of the major axis in the left anterior oblique view. This axis shortened less in patients with an atrial septal defect than in normal adults. However, the degree of shortening in this axis may not be comparable in these two groups. Enlargement of the right ventricle is known to cause rotation of the heart so as to push the left ventricle posteriorly[15]; this change would so alter the left anterior oblique view of the left ventricle that the chord connecting the aortic valve with the "apex" might no longer measure a similar dimension as in normal subjects.

The coexistence of a decreased left ventricular end-diastolic volume and a normal left ventricular end-diastolic pressure is abnormal. This alteration in end-diastolic volume-pressure relation suggests that the left ventricle may be less distensible than normal. To test this possibility further, low molecular weight dextran was given to a patient with atrial septal defect not included in this series. Administration of 500 ml of 10 percent dextran (weight/volume) in 5 percent dextrose in water produced a 100 percent increase in left ventricular end-diastolic pressure (from 6 to 12 mm Hg) associated with a minimal, if any, increase in end-diastolic volume index (59 to 61 ml/m^2). Although the magnitude of change in the left ventricular end-diastolic pressure is not abnormal,[24] the discrepancy between change in pressure and volumes implies that the left ventricle is less distensible than normal at end-diastole.

Decreased distensibility might compromise the ability to increase the preload to the ventricle and thus contribute to the low systemic cardiac index. However the difficulty in adjusting preload may be due simply to the interatrial shunt's ability to limit the volume reaching the left ventricle. We were unable in this study to define the relation of these two possibilities. Nevertheless, the presence of a low systemic cardiac output should ordinarily stimulate some kind of compensatory mechanism to drive the output toward normal. For example, why is there not an increase in venous filling, reduction in systemic impedance or increase in heart rate to compensate for the small left ventricular output? Possible explanations might include a disorder of neural control, or perhaps the existence of pulmonary volume receptors capable of overriding the systemic circuit's signals because of increased flow in the pulmonary vasculature. The results of Epstein et al.[23] show that the limitation on cardiac output response to exercise after

surgical closure of the atrial septal defect is secondary to an inability to increase stroke volume. This observation implies that the left ventricle itself is central to this disorder of hemostasis.

Causes of decreased left ventricular distensibility: If, in fact, the left ventricle has decreased distensibility, what is the cause? It has been suggested[1,5] that the encroachment of a hypertrophied septum into the left ventricular cavity might interfere with left ventricular filling. This has been referred to as a "reversed Bernheim's syndrome." In two patients with atrial septal defect, Harken is said[1] to have palpated the cavity of the left ventricle during exploratory cardiotomy and found that the septum obliterated the cavity. Although no further investigation of the possibility has been reported, echocardiographic analysis of our cases revealed no such obliteration. Furthermore, septal thickness was normal by echocardiography (average 9 mm compared with accepted normal values of 9.7 mm).[25]

Coexistent coronary artery disease might produce a less distensible left ventricle. None of these patients had discernible coronary arterial obstruction. Additionally, no abnormality of left ventricular motion was observed except for that involving the septum (Fig. 5). This abnormality of septal motion seen in angiograms correlates well with the abnormality observed in echocardiograms.

Finally, an increased left ventricular mass or thickness could produce such a postulated decrease in distensibility. Left ventricular thickness is hard to ascertain by angiography in the presence of right ventricular enlargement. However, biventricular angiography allows definition of each ventricular outline and thus an estimation of left ventricular wall thickness separate from that of the right ventricle. Left ventricular mass so determined in three patients was decreased with respect to both body size and left ventricular volume.[26] Echocardiographic analysis of posterior left ventricular wall thickness in another three patients revealed normal findings (average 10 mm, normal 9.1 ± 0.9 [standard deviation] mm).[25] Even from these small numbers of observations, one can state that left ventricular mass is not increased above normal.

Thus, it seems that none of these possibilities adequately explains the existence of decreased left ventricular distensibility. One might hypothesize that lifelong lack of normal stretch induced by normal filling might lead to a less elastic left ventricle.

In conclusion, the presence of abnormal indexes of left ventricular function in these patients suggests that left ventricular dysfunction may be a common finding in adult patients with an atrial septal defect. The superimposition of a mild degree of such stresses as hypertension, age, atrial fibrillation or mitral regurgitation might then result in clinical heart failure. There is abundant evidence that this disorder of left ventricular function persists after the atrial septal defect is surgically closed.

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Phasic Left Ventricular Blood Velocity Alternans in Man

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With use of the Doppler ultrasonic flowmeter catheter, phasic instantaneous left ventricular blood flow velocity was measured by radiotelemetry in 28 subjects during pacemaker-evoked pulsus alternans. Blood velocity alternation was more manifest at faster pacing rates. Four patients demonstrated diastolic blood velocity alternans at the mitral valve. Discordant right heart pressure and left ventricular blood velocity alternation was recorded in three subjects. In one such patient, rate-related shifts of concordant and discordant left ventricular blood velocity alternans occurred. Intermediate or variant forms of alternation, comprising weak and strong beats in a ratio of 2:1, were noted in two subjects.

This study provides the first comprehensive description of left ventricular blood velocity alternans in man. The observed phenomena may be related to an altered inotropic state or to beat to beat variations in end-diastolic fiber length.

Pulsus alternans is a well recognized physical sign of underlying cardiac dysfunction. Most studies of pulsatile alternation have been performed utilizing direct or indirect pressure measurements,[1] left ventricular volume estimation[2] and the assessment of various indexes of myocardial contractility.[3] Furthermore, aortic or peripheral arterial blood velocity alternation has been recorded in a few patients with compromised left ventricular function[4] and in some normal subjects during rapid cardiac pacing.[5]

A recent study from this laboratory[6] has demonstrated the feasibility of directly measuring blood cell velocity in the left ventricle of conscious man by means of Doppler catheter velocimetry. We describe here initial observations of left ventricular blood velocity alternation in human subjects.

Material and Method

Twenty-eight subjects composed the study group. There were 25 men and 3 women whose ages ranged from 17 to 73 years (mean 54). Twenty-one patients had coronary artery disease, three had hypertension, three had no evidence of cardiovascular abnormality and one had primary cardiomyopathy. The three normal subjects were studied because of the presence of chest pain or systolic murmurs that were originally thought to represent heart disease. All diagnoses were established on the basis of complete right and left heart catheterization, selective coronary cineangiography and indicator-dilution curves. Studies were performed with subjects in the postabsorptive state in the supine position. After informed consent was obtained, the right brachial artery and a medial antecubital vein were surgically exposed using local anesthesia (1 percent lidocaine). A saline-filled no. 7 or 8 Zucker bipolar pacing catheter was introduced into the vein and advanced to the right heart chambers for the purpose of obtaining pressures or elective right atrial and ventricular pacing. Pressures were measured by connecting the catheter to a Statham P23Db strain gauge transducer. Pacing was performed with a Cordis Synchrocor pacemaker.

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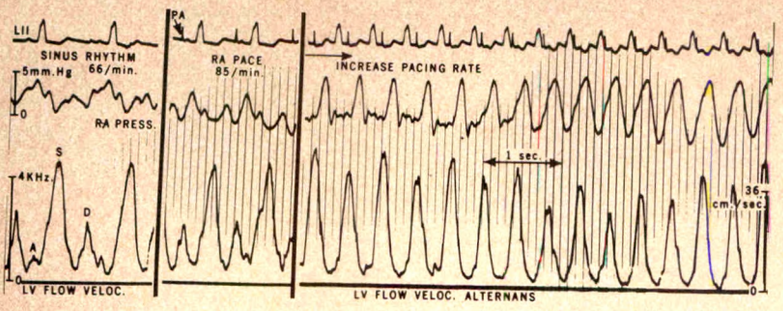

FIGURE 1. Simultaneously recorded lead II (L II) of the electrocardiogram, right atrial pressure (RA PRESS.) and left ventricular (LV) outflow tract blood velocity (VELOC.) in a 48 year old man with coronary artery disease. During sinus rhythm **(left panel)** and right atrial pacing (RA PACE) at a rate of 85/min, **(middle panel)** peak levels of left ventricular blood velocity are stable. Progressive cardioacceleration **(right panel)** results in classic "high-low" alternation of blood velocity. The percent difference between peak velocity levels of strong and weak beats is greatest when the pacing rate is increased rapidly. A = atrial; D = diastolic; PA = pacing stimulus artifact; S = systolic.

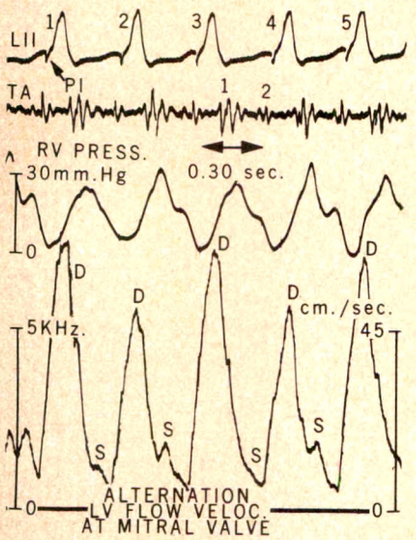

FIGURE 2. Simultaneously recorded lead II (L II) of the electrocardiogram, tricuspid area (TA) phonocardiogram, right ventricular pressure (RV PRESS.) and phasic left ventricular blood velocity at the mitral valve of a 61 year old woman with primary cardiomyopathy. Even-numbered QRS complexes (2 and 4) result in higher peak levels of systolic and diastolic mitral valve blood velocity during right ventricular pacing. Note the concordant peak systolic right ventricular pressure alternation. PI = pacing impulse; other abbreviations as in Figure 1.

Phasic instantaneous left ventricular blood velocity was measured by radiotelemetry utilizing a Doppler flowmeter catheter. Details concerning the method for such measurement have recently been described[6] and can be summarized as follows: The crystal-tipped catheter is passed from the brachial artery to the aorta and advanced across the aortic valve into the left ventricle under constant fluoroscopic image intensification. On the basis of the anatomic site of measurement, three major patterns of left ventricular blood velocity could be distinguished: outflow tract, major systolic ejection wave with smaller diastolic wave; midcavity, biphasic or triphasic blood velocity wave forms; and mitral valve, dominant pandiastolic wave followed by a small systolic component. All blood velocity signals, lead II of the electrocardiogram, right heart pressures, and in a few cases the apex cardiogram, phonocardiogram or external carotid pulse tracing, were simultaneously recorded on a DR-12 Electronics for Medicine oscilloscopic-photographic recorder.

In 23 cases left ventricular blood velocity alternans occurred during the course of right heart pacing at different driving rates. In the remaining subjects, catheter-evoked right ventricular premature depolarizations were electively introduced during cardiac pacing, thereby resulting in postextrasystolic blood velocity alternation.

Results

Critical right atrial or ventricular driving rates required for appreciable left ventricular blood velocity

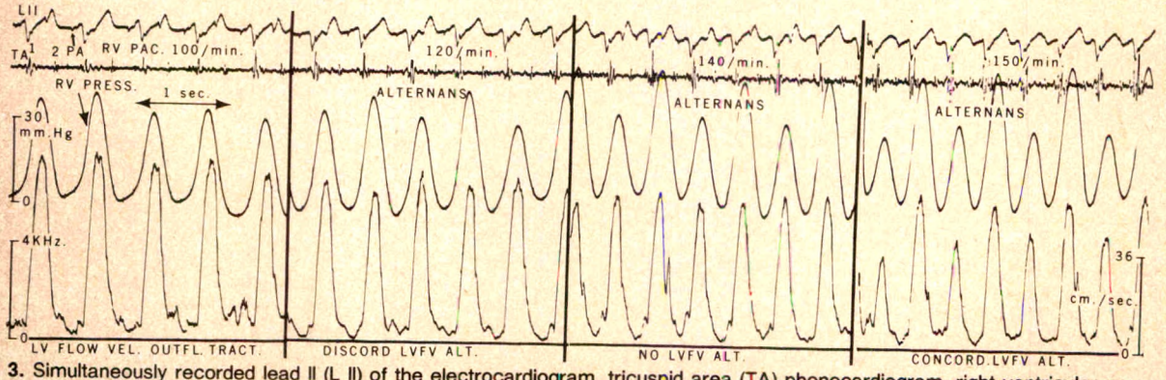

FIGURE 3. Simultaneously recorded lead II (L II) of the electrocardiogram, tricuspid area (TA) phonocardiogram, right ventricular pressure (RV PRESS.) and left ventricular outflow tract blood velocity during right ventricular pacing in a 30 year old man with coronary artery disease. At a driving rate of 120/min **(second panel from left),** discordant alternation occurs. A pacing rate of 140/min **(third panel)** results in right ventricular pressure alternans without concomitant left ventricular blood velocity alternation. Concordant alternation of left ventricular blood velocity and right ventricular pressure unexpectedly occurs at a driving rate of 150/min **(fourth panel).** CONCORD = concordant; DISCORD = discordant; LVFV ALT = left ventricular flow velocity alternans; LV = left ventricular; OUTFL. = outflow; PA = pacing stimulus artifact; RV PAC. = right ventricular pacing; VEL. = velocity.

alternation in 23 subjects ranged from 100 to 160 beats/min. In the vast majority of cases (19 of 23), outflow tract blood velocity alternans of a classic "high-low" nature was more manifest when the heart rates were increased rapidly (Fig. 1). All four patients in whom inflow tract blood velocity was recorded at the mitral valve manifested high amplitude diastolic blood velocity waves followed by low amplitude systolic blood velocity waves for each series of alternating beats. In one of these subjects, concordant peak right ventricular pressure alternans was simultaneously recorded during right ventricular pacing (Fig. 2). When the flow velocity catheter tip was withdrawn from the mitral valve to the outflow tract position it was noted that the low and high amplitude systolic blood velocity waves in the inflow tract correlated with similar systolic alternation at the site of the outflow tract. Such correlation was facilitated by noting the relation of the respective blood velocity wave forms to alternate QRS complexes on a simultaneously recorded electrocardiogram during cardiac pacing and withdrawal of the Doppler catheter.

Discordant alternation: Recordings obtained from three patients demonstrated discordant right ventricular or pulmonary arterial peak pressure alternans; that is, a low peak systolic left ventricular outflow tract blood velocity wave was inscribed at the same time as the higher right ventricular or pulmonary arterial pressure. One subject displayed an unusual variation of discordant biventricular alternans. At lower right ventricular driving rates discordant peak left ventricular outflow tract blood velocity and right ventricular pressure alternation occurred. During more rapid pacing rates the left ventricular blood velocity and right ventricular pressure recordings were in phase, with resulting concordant high-low alternation (Fig. 3). When the pacing rate was reduced within a short period of time, a transition from concordant to discordant alternation was observed (Fig. 4).

Combined electrical and blood velocity alternans: Two subjects manifested combined electrocardiographic and left ventricular blood velocity alternation. In one, a catheter-evoked premature ventricular depolarization produced a period of postextrasystolic electromechanical alternans. Higher amplitude QRS complexes resulted in ventricular contractions that produced reductions in left ventricular outflow tract blood velocity and right ventricular pressure and smaller deflections in the external carotid pulse tracing (Fig. 5). In the second patient, a pacemaker-induced episode of ventricular tachycar-

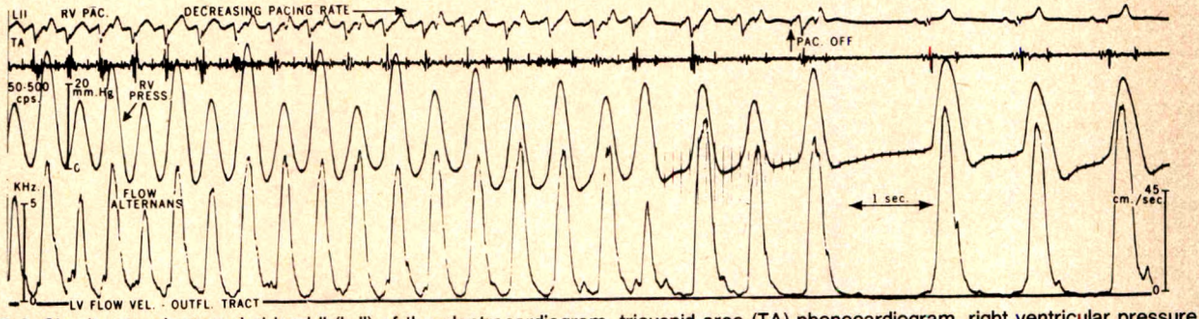

FIGURE 4. Simultaneously recorded lead II (L II) of the electrocardiogram, tricuspid area (TA) phonocardiogram, right ventricular pressure (RV PRESS.) and left ventricular outflow tract blood velocity during a decreasing ventricular pacing rate in a 30 year old man with coronary artery disease. The first seven QRS complexes are associated with concordant right ventricular pressure and left ventricular blood velocity alternans. The eighth and ninth beats result in two peak left ventricular blood velocity waves of equal magnitude, while right ventricular pressure alternans continues. The 10th through 16th beats produce discordant biventricular alternation. Note that the alternans is more prominent during the faster heart rate. PAC. OFF = pacing discontinued; other abbreviations as in Figure 3.

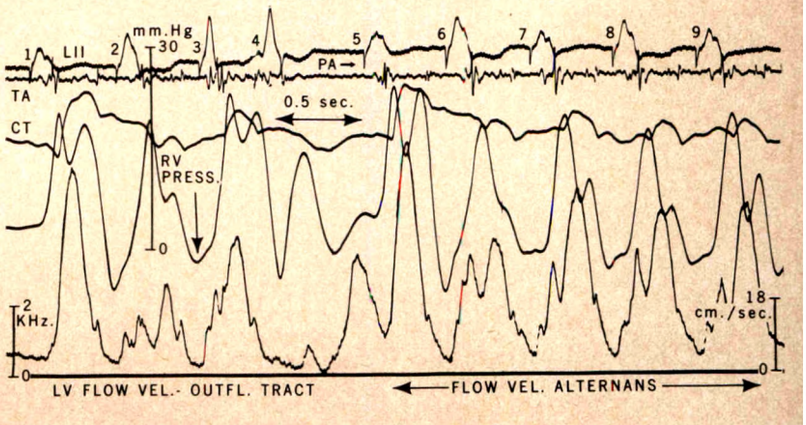

FIGURE 5. Simultaneously recorded lead II (L II) of the electrocardiogram, tricuspid area (TA) phonocardiogram, external carotid arterial pulse tracing (CT), right ventricular pressure (RV PRESS.) and phasic left ventricular outflow tract blood velocity during right ventricular pacing in a 52 year old man with coronary artery disease. A catheter-evoked ventricular premature depolarization (beat 4) results in postextrasystolic electromechanical alternation. Note that the QRS complexes of greater amplitude (6 and 8) are associated with smaller deflections in the carotid pulse tracing, lesser peak right ventricular pressures and lower left ventricular outflow tract blood velocity waves. Abbreviations as in Figure 3.

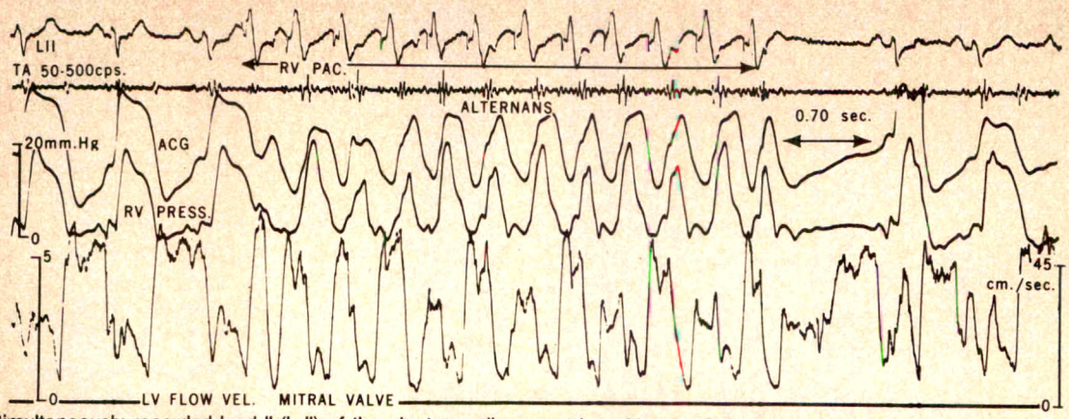

FIGURE 6. Simultaneously recorded lead II (L II) of the electrocardiogram, tricuspid area (TA) phonocardiogram, apex cardiogram (ACG), right ventricular pressure (RV PRESS.) and left ventricular blood velocity at the mitral valve of a 66 year old man with coronary artery disease. Total electromechanical alternans commences with the fourth QRS complex of a pacemaker-induced episode of ventricular tachycardia. Alternating QRS complexes of greater positive polarity are associated with a broader peak plateau in the apex cardiogram, greater right ventricular pressure and larger systolic and diastolic blood velocity waves at the mitral valve. Abbreviations as in Figure 3.

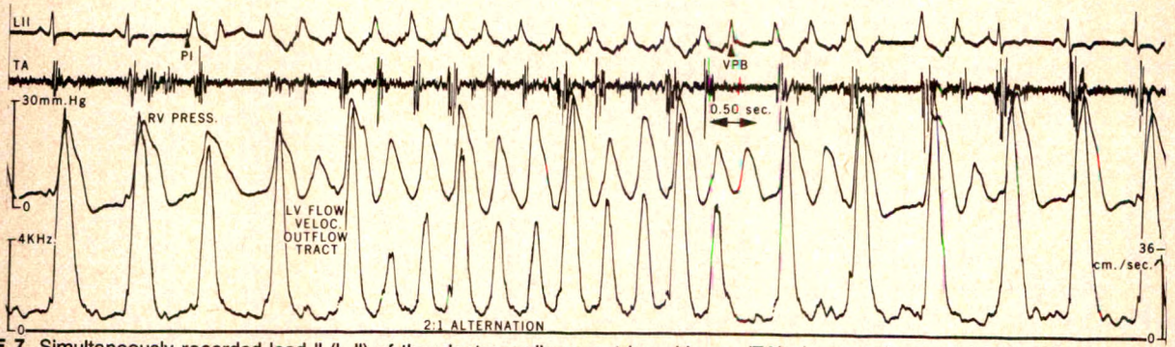

FIGURE 7. Simultaneously recorded lead II (L II) of the electrocardiogram, tricuspid area (TA) phonocardiogram, right ventricular pressure (RV PRESS.) and left ventricular outflow tract blood velocity in a 53 year old man with coronary artery disease. Rapid right ventricular pacing (rate 140/min) results in three periods of variant biventricular alternation. Lower peak right ventricular pressures and peak left ventricular blood velocity waves alternate with beats of greater amplitude in a ratio of 2:1 (that is, every third beat manifests greater amplitude of pressure and blood velocity). The alternation is terminated by a ventricular premature beat (VPB). LV = left ventricular; PI = pacing impulse; VELOC. = velocity.

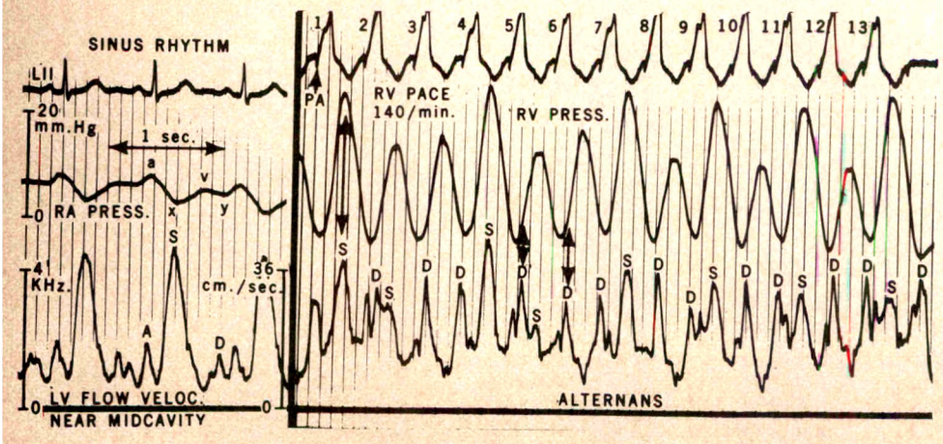

FIGURE 8. Simultaneously recorded lead II (L II) of the electrocardiogram, right heart pressures and left ventricular blood velocity in a 40 year old man with coronary artery disease. **Right panel** shows midcavity blood velocity during right ventricular pacing at a rate of 140/min. Beats 1 to 7 result in right ventricular pressure and left ventricular midcavity blood velocity alternation in a 2:1 ratio. Beats 8 to 13 demonstrate classic "high-low" concordant alternation of pressure and systolic blood velocity. Peak diastolic (D) blood velocity waves remain relatively stable throughout the recording. Note that the highest peak systolic (S) blood velocity and right ventricular pressure waves are associated with more prominently notched QRS complexes. LV = left ventricular; PA = pacing stimulus artifact; PACE = pacing; PRESS. = pressure; RA = right atrial; RV = right ventricular; VELOC. = velocity.

dia effected alternation of the apex cardiogram, right ventricular pressure and left ventricular blood velocity at the mitral valve (Fig. 6).

Variant blood velocity alternans: Intermediate variations of phasic left ventricular blood velocity, unrelated to respiration, were observed in two patients. Low blood velocity waves alternated with high blood velocity waves in a ratio of 2:1. In one such patient, this was the only form of alternation observed and variation of peak blood velocity occurred independently of any identifiable atrial contractions during the course of ventricular pacing. In addition, there was concordant 2:1 right ventricular pressure alternans (Fig. 7). One 40 year old man with coronary artery disease manifested an unusual variant of left ventricular blood velocity alternation (Fig. 8). A sustained period of alternation composed of low and high amplitude biventricular systolic beats in a ratio of 2:1 abruptly evolved into classic "high-low" alternans. At the same time, those beats of greatest amplitude were generated by QRS complexes with prominent notching.

Discussion

This report represents the first comprehensive description of blood velocity alternation within the left ventricle of man. Continuous measurements of aortic[4] and peripheral arterial[5] blood velocity waves in patients during natural and pacemaker-evoked arrhythmias have demonstrated that larger pulse amplitudes during the course of pressure alternation were associated with greater peak blood velocity in these vessels. The results described here indicate that these beat to beat fluctuations of blood flow are based on alternating levels of blood cell velocity within the left ventricle. Accentuation of left ventricular blood velocity alternans during increasing heart rate can be ascribed to greater disparity in end-diastolic fiber lengths[2,7] or differences in inotropic state[3] during cardioacceleration.

Blood velocity alternans in the left ventricular inflow tract: Of interest was alternation of the blood flow velocity recorded in the left ventricular inflow tract at the mitral valves of four subjects. Stronger beats produced both larger systolic and strikingly greater diastolic inflow tract blood velocity waves. The larger systolic waves represented forward ejection velocity at the mitral valve, sensed by the crystal-tipped catheter.[6] On the other hand, augmented diastolic waves during ventricular pacing in the absence of coordinated atrioventricular contraction, suggested either changing mitral valve areas, more rapid diastolic left ventricular expansion or greater left ventricular relaxation[3,7] after stronger beats of pulsus alternans. This study did not determine the mechanism responsible for this phenomenon, and further investigation of alternating levels of left ventricular filling velocity appears warranted.

Biventricular alternans: Concordant aortic blood velocity, right ventricular pressure and right atrial blood velocity alternation have been previously noted in man.[8] In addition, there have been reports of independent pulsus alternans in the greater and lesser circulations.[9] Recordings obtained from one subject described in this study demonstrated a rate-related transition of discordant to concordant biventricular alternans. In this patient, alternation of right ventricular end-diastolic fiber length or contractile force was a constant feature during rapid ventricular pacing. At critical heart rates, discordant left ventricular blood velocity alternation evolved into a state in which left ventricular contractions were presumably of equal magnitude. When the pacing rate was increased, left ventricular contractions began to alternate again and blood velocity came into phase with strong and weak right ventricular beats. These observations suggest that varying right or left ventricular blood velocity alternation, concordant or discordant, can be manifested in a variety of ways, dependent on the heart rate and inotropic state of each ventricle. In 1960, McIntosh[10] described recordings from a patient with right ventricular pressure alternation and a subtle shift of concordant to discordant brachial arterial alternans. These changes occurred during a stable heart rate and were attributed to unequal ventricular distension after summation of diastolic filling and a larger residual volume in either ventricle.

Variant or intermediate forms of left ventricular blood velocity alternation: These forms of alternans are particularly noteworthy and may represent a "warm-up" phase preceding established pulsus alternans. Demonstration that the last high peak left ventricular blood velocity wave in a cycle of 2:1 alternation was the first strong beat in succeeding classic pulsus alternans lends credence to this proposition. Other variations of the same phenomenon may occur, but we have encountered only weak and strong left ventricular contractions with corresponding low and high peak blood velocity waves in a ratio of 2:1.

The underlying mechanism for pacemaker-induced electrocardiographic alternation with concomitant left ventricular blood velocity alternans is unclear. In general, electrical alternation is frequently accompanied by pulsus alternans whereas the reverse relation is unusual.[11] It is possible that alternating intramyocardial tension and coronary blood flow in some manner render a portion of the myocardium more refractory to depolarization during every other beat.

Clinical implications: The limitations and advantages of Doppler flowmetry for the measurement of phasic instantaneous left ventricular blood velocity have previously been discussed in detail.[6] Furthermore, the conditions producing blood velocity alternans in this study were mainly artificial in nature. In the case of classic alternation, the results described here represent electively induced models of the naturally occurring phenomenon that has been noted during various forms of tachycardia. Further investigation will be required to identify other more unusual

forms of alternans during clinically encountered tachyarrhythmias. Application of this technique provides insight into the varied expression of left ventricular blood cell velocity alternans.

Acknowledgments

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The Coronary Arteries in Marfan's Syndrome

A Morphologic Study

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The coronary arteries of five hearts of patients known to have had Marfan's syndrome were studied microscopically. In four of the five cases the extramural coronary arteries showed structural changes consisting of accumulations of acid mucopolysaccharides and a concomitant disruption of the connective tissue elements. These changes closely resembled the changes that frequently occur in the aorta and that are generally described as "cystic medial necrosis." They are considered to be an important expression of wall weakening. In one case a laceration, probably traumatic, of a coronary artery led to formation of an "incomplete dissecting aneurysm."

"Cystic medial necrosis" was found once in the proximal segment of the sinus nodal artery and once in the musculoelastic layer of a coronary artery that reached the atrioventricular node from the ventricular septum by perforating the anulus fibrosus. However, in contrast to findings in a previous report, the intramural coronary arteries were otherwise unaffected. The clinical significance of these data is as yet unknown particularly since these alterations are intramural and initially do not cause narrowing of the lumen. Nevertheless, the possibility of coronary arterial involvement by the metabolic disorder of Marfan's syndrome should always be considered during clinical assessment of this lesion.

Myocardial ischemia in patients with Marfan's syndrome is most frequently caused by a dissecting aneurysm of the ascending aorta that encroaches upon the segment of origin of a coronary artery. Thus far, only one case of Marfan's syndrome has been recorded in which a *primary* dissecting aneurysm of a coronary artery was observed.[1] However, many reports of cardiac manifestations of Marfan's syndrome give scant mention to the state of the coronary arteries. To the best of our knowledge, only James et al.[2] have considered in detail the pathology of coronary arteries in this disease. They reported that the smaller intramyocardial arteries showed alterations characteristic of an obliterative process; these changes were particularly prominent in the sinus nodal and atrioventricular nodal arteries of the two hearts they studied.

Our interest in the condition of the coronary arteries in Marfan's syndrome was initiated by the admission of an 18 year old woman with Marfan's syndrome into our Department of Cardiology. This patient had aortic and mitral valve insufficiency complicated by severe angina pectoris that could not be explained solely on the basis of augmented myocardial demand. On clinical grounds, aortic dissection seemed unlikely. Our clinical colleagues' question—"Are the coronary arteries involved in Marfan's syndrome?"—and their report on the lack of published data on this subject prompted this investigation of the coronary arteries in five hearts from patients with Marfan's syndrome.

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Material and Methods

The study comprises a morphologic investigation of five hearts from patients with Marfan's syndrome. Four of the five patients were men aged 21, 23, 29 and 32 years, respectively. The one woman in this series was 51 years of age. All five patients had the characteristic features of Marfan's syndrome and were admitted to the hospital with a dissecting aneurysm in a markedly dilated ascending aorta and with signs of aortic valve incompetence. None of the five patients had rhythm or conduction disturbances. Two patients underwent combined reconstructive surgery for their aneurysm and insertion of an aortic valve prosthesis. One patient (Case 5) died in the immediate postoperative peri-

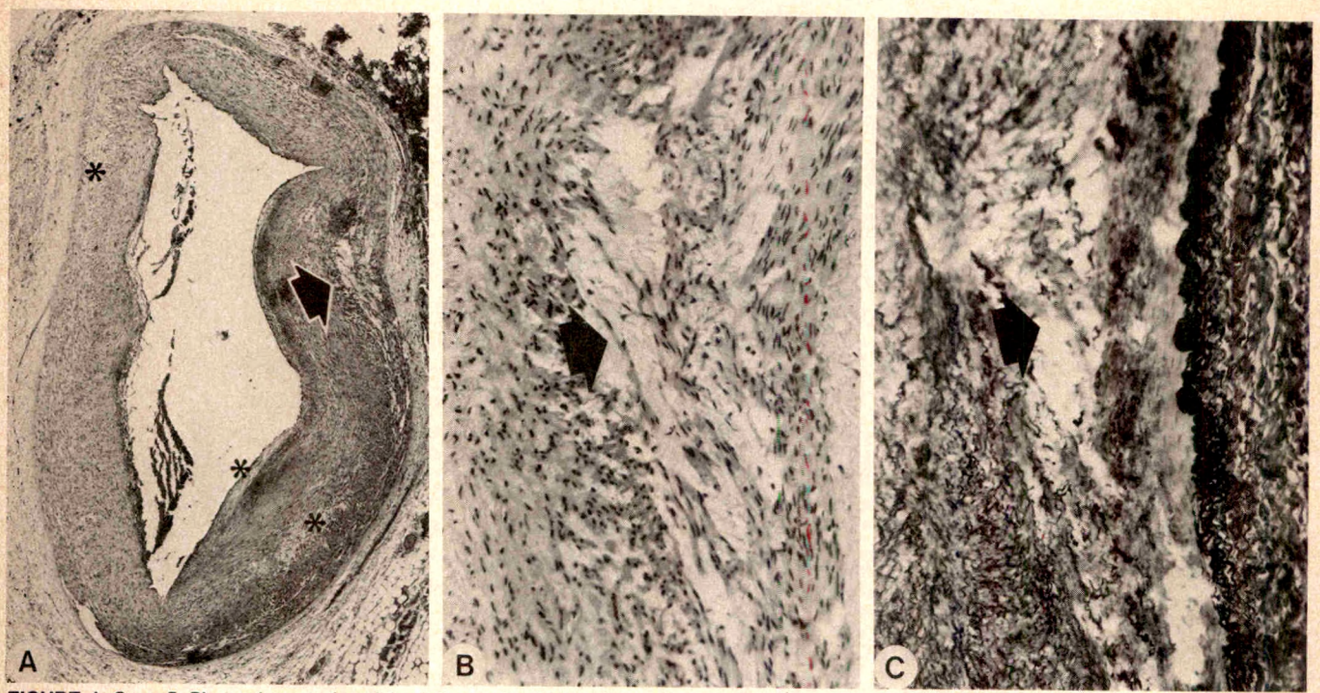

FIGURE 1. Case 5. Photomicrographs of the left anterior descending coronary artery. **A,** cross section showing several pools of mucopolysaccharides in both the media and the intima with disruption of the normal wall structure **(*).** In one area extensive separation of the muscular layer by mucoid material is apparent **(arrow). B,** detailed view of area indicated by **arrow** in **A.** It clearly shows mucoid pools separating the cellular elements of the media **(arrow). C,** the same area shown in **B** prepared with an elastic tissue stain. There are disruption and fragmentation of the elastic fibrils in the media and pooling of mucoid material in that particular area **(arrow).** (**A** and **B,** hematoxylin-eosin stain ×25 and 140, respectively; **C,** elastic tissue stain ×140. All reduced by 27 percent.)

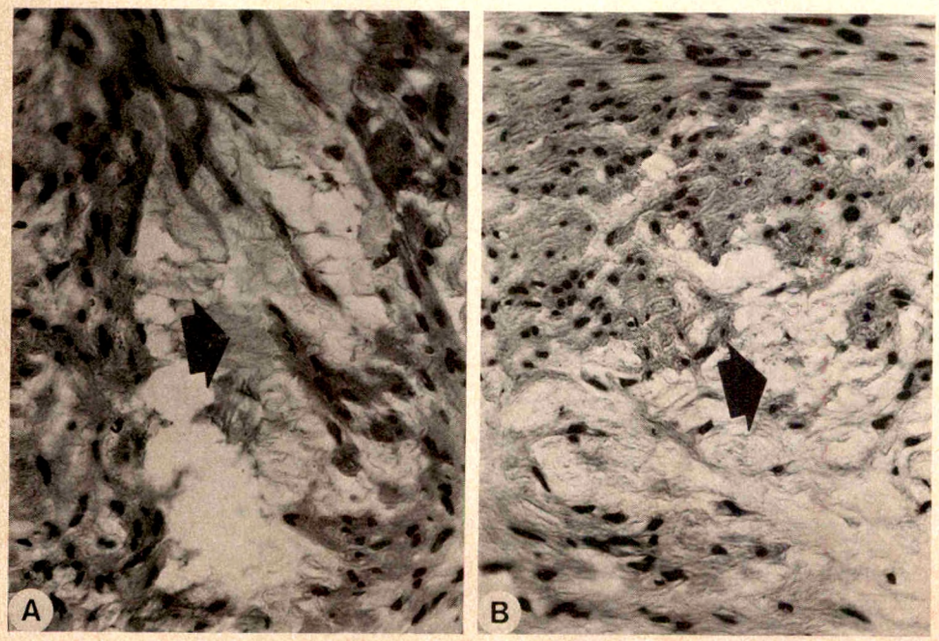

FIGURE 2. A, Case 1. **B,** Case 2. Photomicrographs showing pools of mucoid material that have accumulated in the media of the extramural coronary arteries. The separation of muscular elements and disruption of the connective tissue components is evident **(arrows).** (Hematoxylin-eosin stain ×350 [**A**] and 140 [**B**], reduced by 26 percent.)

od from a recurrent aortic tear. Another (Case 3) had an anteroseptal myocardial infarction after surgery and died 2 months later from progressive pump failure. The three other patients were being medically treated in the hospital when they died as a result of cardiac tamponade caused by a ruptured aneurysm.

Autopsy findings confirmed the clinical diagnosis in each instance. In no instance did the aortic dissection encroach upon the coronary arteries themselves, although there was a marked narrowing of the lumen of the proximal segments due to compression by the hematoma.

Pathologic studies: The coronary arteries were completely sectioned along their epicardial course at intervals of approximately 3 mm. Sections were taken whenever gross inspection of the cut surfaces revealed an abnormality. In addition, routine sections were taken in each case from (1) the main stem of the coronary artery, (2) the proximal segment of the anterior descending artery at a point 1 cm from its origin, (3) the proximal segment of the left circumflex artery at a point 1 cm from its origin, and (4) from the right coronary artery at a point approximately 1 cm from its aortic origin. The areas of the sinus and atrioventricular nodes were sectioned in blocks and studied microscopically in each case. In addition, both the sinus nodal artery and the atrioventricular nodal artery were dissected grossly and routine sections taken from their proximal segments. The intramural arteries were studied in sections of the left ventricular myocardium taken (1) anteriorly near the apex, and (2) posteriorly near the crux cordis.

The sections were stained with either hematoxylin-eosin or an elastic tissue stain. Additional stains such as the alcian blue stain for acid mucopolysaccharides and combinations of this technique with connective tissue stains and the periodic acid-Schiff stain were applied as deemed necessary.

Results

The observations with respect to the extramural and intramural coronary arteries in the five hearts are summarized in Table I.

TABLE I

"Cystic Medial Necrosis" in the Coronary Arteries in Marfan's syndrome

Case no.	Age (yr) & Sex	LCA	LAD	LCx	RCA	SNA	AVA	Intramural Arteries
1	21M	—	—	—	+	+*	—	—
2	23M	+	+	+	+	—	—	—
3	29M	+†	+	+	+	—	—	—
4	32M	—	—	—	—	—	—‡	—
5	51F	+	+	+	+	—	—	—

*"Cystic medial necrosis" present only in proximal segment of artery.

†This segment was further complicated by an "incomplete dissecting aneurysm."

‡"Cystic medial necrosis" present in a coronary artery that penetrated the node from the ventricular septum.

+ = present; — = absent.

AVA = atrioventricular nodal artery; LAD = left anterior descending coronary artery; LCA = left main coronary artery; LCx = left circumflex artery; RCA = right coronary artery; SNA = sinus nodal artery.

Extramural coronary arteries: In four of the five hearts changes were observed in the extramural coronary arteries (Fig. 1). These changes were primarily confined to the media but were also present in the musculoelastic layer of the intima (Fig. 1). They were characterized by accumulations of a mucoid material that gave a positive reaction with alcian blue staining, indicating the presence of acid mucopolysaccharides. At the site of these accumulations the normal appearance of the arterial wall was disrupted (Fig. 1 and 2). In some instances, only the smooth muscle cells of the media were separated, whereas the

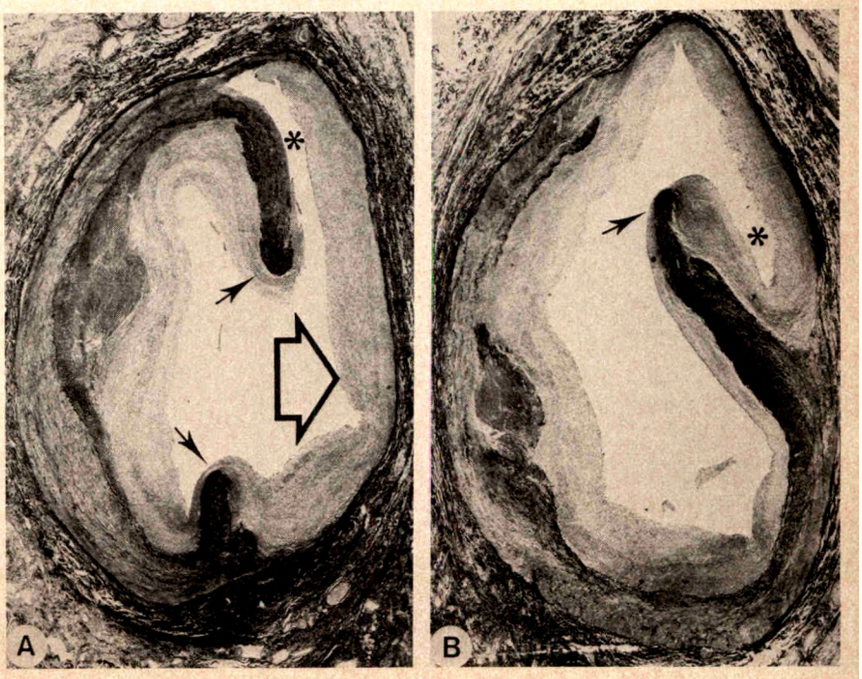

FIGURE 3. Case 3. Photomicrographs of cross sections of the left main stem artery. The artery shows an abrupt laceration of the media **(arrows)** with a partial dissection **(*)** and aneurysmal dilatation **(open arrow).** The outer wall at the latter site consists of adventitia and remnants of the disrupted media. The wall on the luminal aspect is composed of loosely arranged, vascular connective tissue, which has the features of organized thrombosis. (Elastic tissue stain ×25, reduced by 27 percent.)

collagen and elastic fibrils seemed intact. In other instances, the changes were more pronounced. These areas revealed actual disruption of connective tissue fibers together with the formation of pools of mucoid material and fine fibrillar material that produced wide separation in the muscular layer (Fig. 2). The internal elastic lamina at these sites also showed irregular fragmentations, and occasionally the mucoid material of the media was continuous by way of these interruptions with similar pools within the musculoelastic layer of the intima. The musculoelastic layer otherwise showed no distinction from the layer normally encountered.

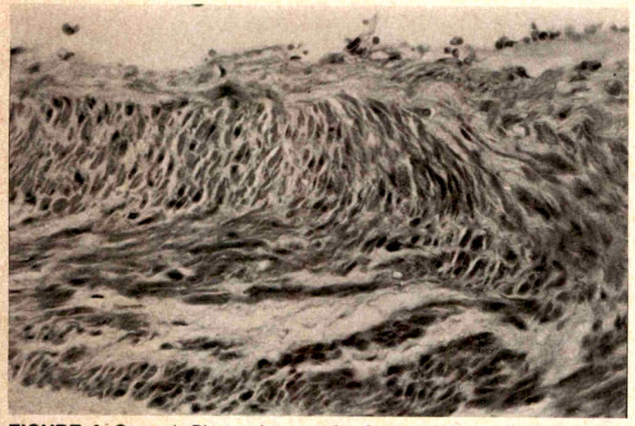

FIGURE 4. Case 1. Photomicrograph of part of the wall of the sinus nodal artery, just after its origin from the right coronary artery. The section shows a moderate accumulation of mucoid material in the media with disruption of the muscular layer. The artery no longer showed this abnormality when sectioned more peripherally. (Hematoxylin-eosin stain ×350, reduced by 31 percent.)

When present, the mucoid changes described were observed in most of the extramural coronary arteries (Table I). In one instance (Case 3) a complicated lesion was encountered in the main stem of the left coronary artery. This lesion consisted of an abrupt laceration of the wall together with incomplete rupture of the vessel and aneurysmal-like dilatation (Fig. 3). The outer wall of this dilated arterial segment consisted only of adventitia and sparse remnants of the disrupted media (Fig. 3). The wall on the luminal aspect was composed of loosely arranged and highly vascular "young" connective tissue (Fig. 3). The patency of the artery was considerably reduced by this lesion. The media in this particular segment exhibited some of the previously described mucoid accumulations. Such accumulations became particularly pronounced beyond the bifurcation in the proximal parts of both the left anterior descending and the left circumflex coronary arteries. These two vessels were not otherwise changed. The heart showed a large anteroseptal infarction that extended onto the lateral wall of the left ventricle, producing involvement of the anterolateral papillary muscle.

Sinus nodal artery: In only one instance in this series was the sinus nodal artery affected (Case 1). The vessel showed a moderate accumulation of acid mucopolysaccharides in the media, together with a slight increase in fine fibrillar connective tissue content and some separation of muscle cells (Fig. 4). The intima of the artery showed a musculoelastic layer of normal configuration and structure. The segment of the artery thus involved was close to the origin from the main right coronary artery. Inside the sinus node itself, however, the artery did not reveal any of these changes. The sinus nodal artery in the remaining four

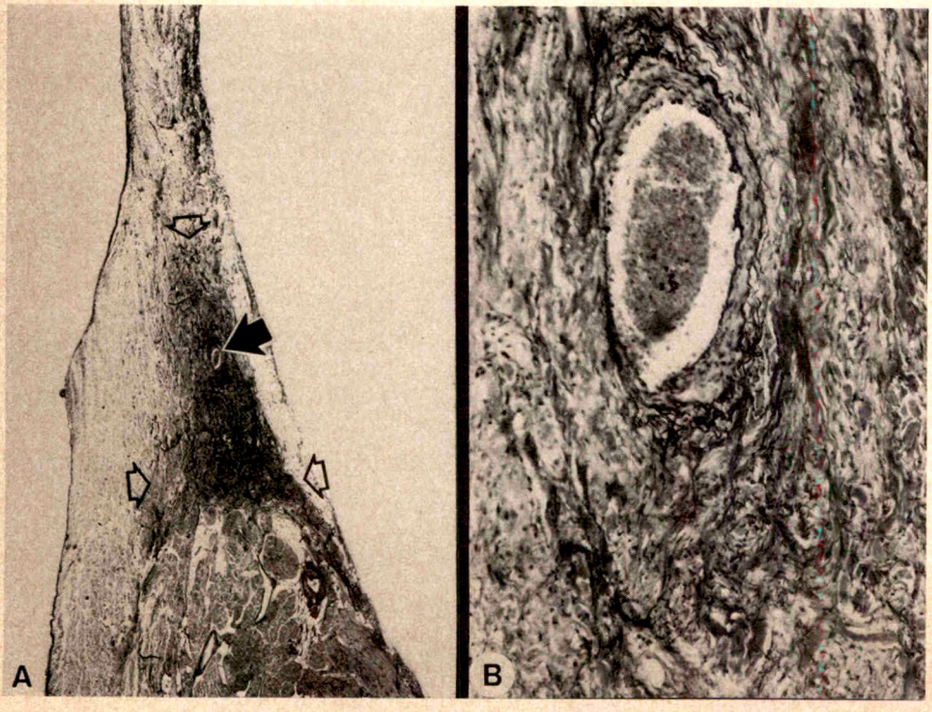

FIGURE 5. Case 5. Photomicrographs of the sinus node and embedded sinus nodal artery. **A,** the nodal area **(light arrows)** shows the normal arrangement for a young person. The sinus nodal artery **(solid arrow)** is normally positioned. **B,** detail of sinus node and its nutrient artery. The latter is normal in structure. The node itself shows a compact arrangement without mucoid pooling, consistent with young age. (Elastic tissue stain ×15 **[A]** and 140 **[B]**, reduced by 23 percent.)

hearts was normal in both its extranodal and intranodal course (Fig. 5).

Atrioventricular nodal artery: The segment of the atrioventricular nodal artery that originated from the U loop at the crux cordis showed a normal muscular structure in each case. A musculoelastic layer was always present and continued in the arterial segment that ramified within the node. It was of interest that a moderately large artery, which penetrated the fibrotic anulus from the ventricular septum toward the atrioventricular node, always exhibited a markedly pronounced musculoelastic layer. Furthermore, this layer originated rather abruptly when the artery came close to the fibrotic anulus and continued to be present in the penetrating segment and in part on the atrial aspect of the anulus (Fig. 6). In one instance (Case 4) the artery showed a pool of mucopolysaccharides that separated the elastic fibrils in the musculoelastic layer (Fig. 7). In the remaining four cases this change was not observed.

Intramural coronary arteries: The intramural coronary arteries were normal in each case. Only in the immediate environs of an infarct (Case 3) was intimal fibrosis noted. Mucoid changes or obliterative intimal proliferations were not observed.

Discussion

Pathogenesis of coronary arterial lesions: Our study revealed that the coronary arteries may indeed exhibit pathologic lesions in patients with Marfan's syndrome. In fact, four of the five hearts studied revealed a structural abnormality in the vessel walls (Table I). The abnormality consisted of an accumulation of acid mucopolysaccharides within the vessel

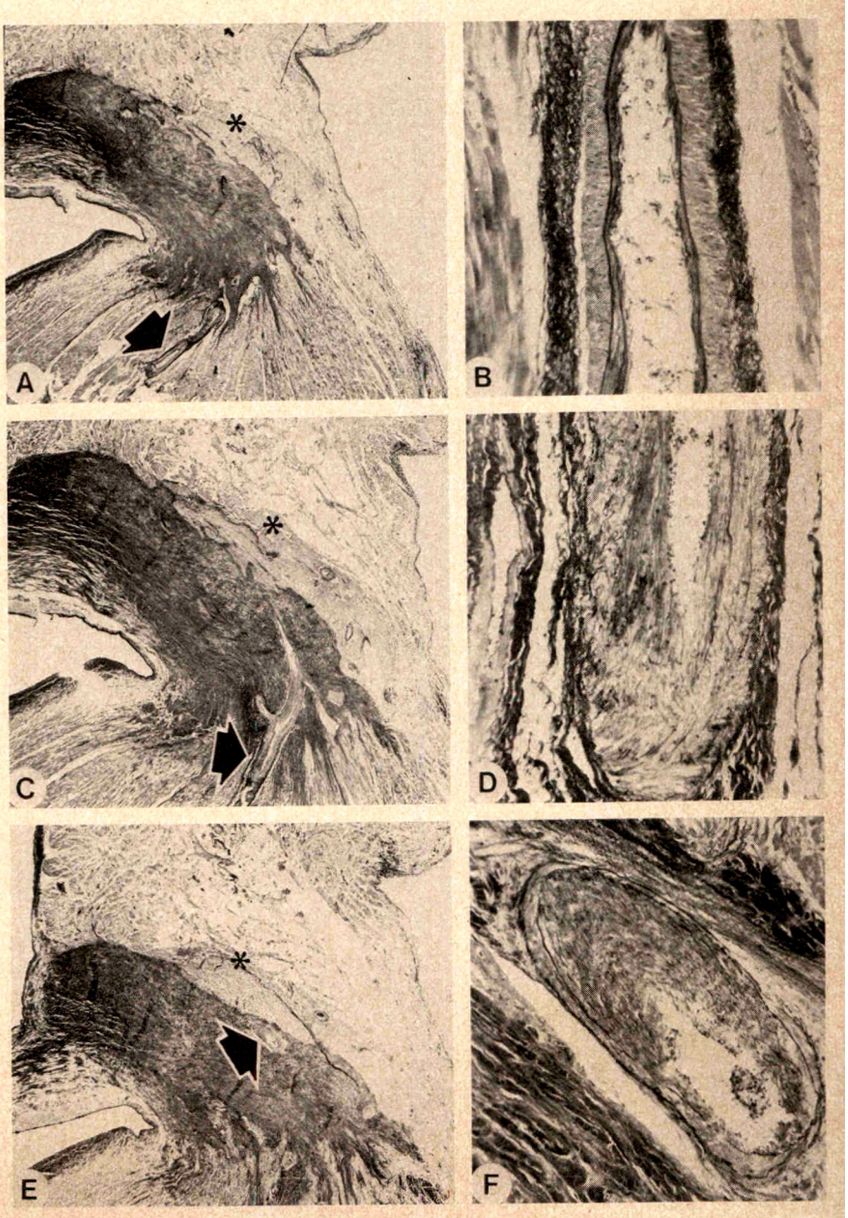

FIGURE 6. Case 5. Photomicrographs of successive sections of the atrioventricular nodal area showing the structural changes in a septal coronary artery **(arrows)** that penetrated the anulus fibrosus on its way to the atrioventricular node **(*)**. **A** and **B,** the artery is approaching the anulus fibrosus and is of a normal muscular type. **C** and **D,** the same artery has penetrated the anulus fibrosus. Its structure has altered, and there is now a marked musculoelastic intimal layer. **E** and **F,** the artery has nearly traversed the anulus fibrosus and is in close apposition to the atrioventricular node. The marked musculoelastic intimal layer is still present. The thickness of this layer is exaggerated since the artery is tangentially sectioned. (Elastic tissue stain ×15 **[A, C** and **E]** and 140 **[B,D** and **F]**, reduced by 27 percent.)

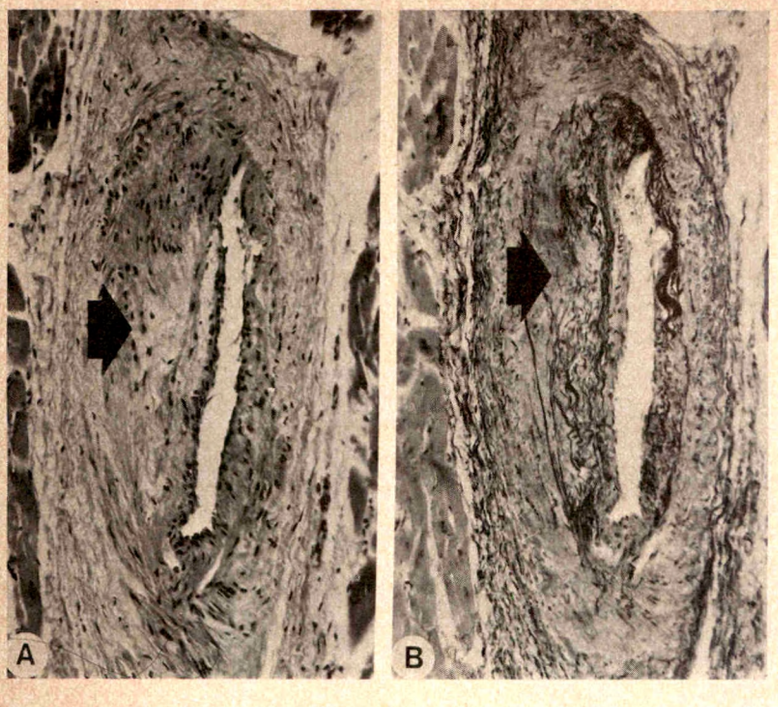

FIGURE 7. Case 4. Photomicrographs of septal coronary artery near the anulus fibrosus. **A,** the artery shows a pool of mucopolysaccharides **(arrow)** in the musculoelastic intimal layer. **B,** the elastic tissue stain of the same area shows a disruption of the elastic fibrils at that particular site **(arrow).** (Hematoxylin-eosin stain [**A**] and elastic tissue stain [**B**] ×140, reduced by 25 percent.)

walls, accompanied by disruption of connective tissue elements. This latter feature was less pronounced than that found in the extensive lesions that may occur in the aorta in Marfan's syndrome. However, although the coronary arteries are of a muscular type and normally possess only sparse connective tissue fibrils, the histologic findings of pooling of acid mucopolysaccharides with disruption of the preexisting wall structure were similar to those observed in the aorta. It is usual to classify such alterations as "cystic medial necrosis." [3]

The pathogenesis of this alteration in Marfan's syndrome is still a matter of dispute, although it is generally agreed that it is in some way related to the metabolic disorder affecting the connective tissues.[4] It should be stated, however, that "cystic medial necrosis" as such is present in the normal aging aortic wall[5,6] and in the pulmonary arteries in cases of long-standing pulmonary hypertension[7,8]; it has also been described in some cases of dissection of a coronary artery unrelated to Marfan's syndrome.[9–11] The "cystic medial necrosis" in Marfan's syndrome is already present at an early age and then to an extensive degree. We therefore feel justified in interpreting the changes in our specimens as an expression of the underlying metabolic disorder that was known to be present.

One may speculate on the possibility that similar changes in the coronary arteries previously described in young persons, whether or not accompanied by a dissection, are indeed "formes frustes" of Marfan's syndrome.[10,12] The structural changes observed in our specimens were particularly prominent in the extramural coronary arteries. As far as we are aware, this feature of Marfan's syndrome has not been specifically reported previously. It is only in a review article of the pathology of angina pectoris that Vlodaver et al.[13] mentioned a case of Marfan's syndrome with "changes of cystic nature" in the media of the coronary arteries, associated with focal fibrous thickening of the intima.

James et al.[2] described obliterative proliferative changes in the intramural coronary arteries in Marfan's syndrome but made no mention of any abnormality of the extramural coronary arteries. In this study we found only one specimen in which the proximal segment of the sinus nodal artery showed degenerative changes, although without appreciable narrowing of the lumen; the artery was normal when embedded within the node itself. However, our five cases were randomly selected cases of Marfan's syndrome, in which no patient had disturbances of rhythm or atrioventricular conduction. In contrast, the two cases of James et al.[2] were particularly selected and studied for these latter reasons. The atrioventricular nodal artery in our five cases was also normal, again in contrast to findings in the cases reported by James et al.[2] The vessel did exhibit a distinct musculoelastic intimal layer. However, we interpret this feature as a normal occurrence. In one instance the arterial branch from the ventricular septum that normally perforates the anulus fibrosus to reach the atrioventricular node showed an accumulation of acid mucopolysaccharides within the musculoelastic layer. We believe that this constituted an abnormality that could be related to the underlying connective tissue disorder.

Coronary dissecting aneurysms: We believe that the "cystic medial necrosis" as encountered in the coronary arteries in these cases is an expression of an affected arterial wall. As such, its presence could indicate an intrinsic weakening of the vessel, which

could therefore be more easily lacerated. This view is in accordance with recent opinions on the development of so-called spontaneous laceration lesions of the aortic wall.[6,14] Indeed, in one of our five cases a complicated lesion of the left coronary main stem fulfilled the histologic criteria for such spontaneous lesions. The media of this artery showed an abrupt interruption of its wall with the formation of an aneurysm. The outer wall of the aneurysm was composed of remnants of the outer layer of the preexistent media, further strengthened by adventitia. When reconstructed from the many slides taken, the lesion could be considered to have resulted from a broad tear in the inner wall which had then expanded to form a saccular aneurysm. Lesions of this type in the aortic wall have been classified as "incomplete dissecting aneurysms." [6,14–16]

As far as we are aware, this case is the first documentation of this lesion in a coronary artery. It is most likely that the laceration that affected the vessel was caused during reconstructive surgery on an aneurysm of the ascending aorta 2 months before the patient's death. The broad layer of newly formed intima that covered the remnants of the media is consistent with a time lag of 2 months and is a recognized feature of long-standing complete and incomplete dissecting aneurysms of the aorta.[17] The occurrence of an incomplete dissection in a coronary artery in a patient with Marfan's syndrome illustrates that these arteries can be vulnerable to trauma, probably as a result of the same mechanisms that render the aorta so vulnerable.

Clinical implication: The finding of the changes of "cystic medial necrosis" in three other cases indicates that these arteries also had the potential for laceration. In our opinion, the latter complication is the major hazard of coronary arterial involvement in Marfan's syndrome since the lesions are intramural and initially do not cause narrowing of the lumen. The latter could also account for the rarity of functional coronary artery disease among the cardiovascular complications of Marfan's syndrome. Nevertheless, our findings indicate that, morphologically, the coronary arteries are indeed involved by a process similar to that affecting the aortic wall. Therefore, the possibility of coronary arterial involvement should always be considered during the clinical evaluation of the patient with Marfan's syndrome.

Acknowledgment

We thank our clinical colleagues of the University Department of Cardiology, Wilhelmina Gasthuis, who suggested the need for this study, and Mrs. H. J. Dijk for the histologic sections and Mr. R. E. Verhoeven for the photographs.

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Clinical Applications of the Threshold Tracking Pacemaker

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The concept of automatic threshold tracking is the most recent adaptation of artificial cardiac pacemakers to physiologic needs. Earlier pacemaker innovations were primarily in the area of timing of impulse delivery, whereas more recent changes have focused on alteration of the amplitude and duration of the pacemaker stimulus. Matching of this stimulus to the cardiac excitation threshold is important because a stimulus greater than necessary is wasteful of battery energy and may produce arrhythmias, whereas a stimulus of less than threshold intensity fails to pace the heart. Because of the wide range of clinically encountered threshold levels it is impossible to design a fixed output pacer that is efficient and safe for all patients at all times.

The threshold tracking pacemaker searches for and finds the threshold level, and adjusts its stimulus to just above this level. The device ensures an adequate safety margin of stimulation, but reduces the stimulus level to the lowest safe level possible. It is fully automatic, adjusts immediately to any threshold changes and is not dependent on manual alteration.

The threshold tracking pacemaker (supported by Vitatron Medical, B.V.) represents a new generation of pacemaker with automatic control of the pacemaker stimulus. It repeatedly searches for and finds the threshold level and adjusts its stimulus to just above this level, ensuring an adequate safety margin and continuous effective pacing but reducing the stimulus to the lowest safe level possible. This device is fully automatic, adjusts immediately to any threshold changes and is not dependent on manual alteration. It was tested clinically in six patients and performed according to specifications. Much additional testing is necessary before the instrument is certified for widespread use, but it appears to offer a significant advance in artificial cardiac pacing.

Instrumentation

A detailed description of the threshold tracking pacemaker has been previously reported.[1] The prototype unit has a range of 0 to 15 milliamperes and is a constant current ventricular-inhibited device. Its essential feature is its capacity to sense for presence or absence of ventricular response (QRS complex) during a 20 to 40 msec period after each pacemaker stimulus. If the pacemaker output is above threshold level, the stimulus amplitude is reduced by 0.5 milliampere decrements until a stimulus fails to evoke a ventricular response, with threshold lying between the last suprathreshold stimulus and the subthreshold stimulus. When the stimulus is reduced to below threshold level, the absence of a response is detected, and 40 msec after the subthreshold stimulus another (backup) stimulus is delivered that is 0.5 milliamperes greater and 1.0 msec longer in duration (Fig. 1). Because the backup stimulus is greater in current and duration than the subthreshold stimulus, it should be great enough to evoke a ventricular response unless there has been a sudden increase of threshold since the previous beat. As a safety feature, if the backup stimulus does not elicit a response, a second backup stimulus with a

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further 0.5 milliampere increment is delivered 40 msec after the first backup pulse.

Continuous and programmed modes: In the prototype model there are two operating modes, continuous and programmed. In the continuous mode, the cycle of testing for threshold is continuously repeated. The pacemaker probes down to lower output levels to determine threshold, provides output at a level above threshold, and then repeats the cycle. When threshold is stable, one test cycle spans three heartbeats and four pacer stimuli (one subthreshold pulse) (Fig. 1). In the programmed mode, the pacemaker determines threshold and sets the output at a preset safety margin (0.5 milliamperes) above threshold level. The output is then kept constant unless an elevation of threshold results in a stimulus that does not produce a response, in which case a second stimulus of greater amplitude and pulse duration is delivered 40 msec after the subthreshold stimulus. The system is automatically reset to the higher stimulus level to compensate for the higher threshold. In the programmed mode the pacemaker does not continuously search for threshold but is programmed to search automatically for threshold at time intervals set by the operator (every 30 seconds or every 2 or 8 minutes) (Fig. 2). In either the continuous or programmed mode, a subthreshold stimulus at any time is followed by a backup stimulus that is above threshold level (or two backup stimuli if necessary). Only with the rare exception of a sudden and pronounced rise in threshold, such as can be produced by pulling back the pacing catheter, are the backup stimuli insufficient to evoke a response.

Methods

After the system was proved feasible and safe in animals,[1] it was tested seven times in six patients. Five of the patients had complete heart block, and one patient was undergoing pacing for control of arrhythmias. In four of the tests the electrode system included a standard bipolar temporary pacing catheter positioned in the apex of the right ventricle and an indifferent electrode plate attached to the right arm. In three tests we used a tripolar electrode with two electrodes spaced 1 cm apart at the distal tip and the third (indifferent) electrode 23 cm back from the distal tip.[2] In all tests pacing was between the distal (cathode) and indifferent (anode) electrodes, with sensing between the proximal of the bipolar pair and the indifferent electrodes.

The threshold tracking pacemaker was tested in each patient for proper sensing and stimulation under several conditions—at rest, with forceful breathing and with the patient in various positions. In three of the seven tests the pacing catheter was inserted at the time of the test, and the system was monitored during positioning of the catheter in the right ventricular apex and during manipulation of the catheter tip to different sites within the right ventricle. All these maneuvers were attempts to produce sudden changes in threshold that would test the ability of the pacemaker to react with the appropriate change in output.

Results

In the first two patients testing was incomplete because of sensing problems that developed when the pacemaker output was at a high level. Redesign of the circuitry corrected this problem and subsequent patient testing yielded successful results. Each patient underwent pacing for 30 to 60 minutes without complication or malfunction. The pacemaker performed to the designed specifications of sensing all

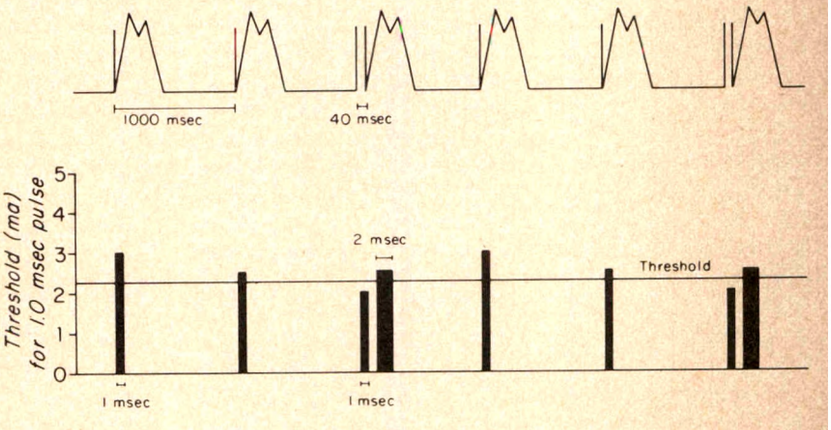

FIGURE 1. Scheme of operation of threshold tracking pacemaker. **Above,** electrocardiogram. **Below,** stimulus output (milliamperes) of pacemaker. Threshold is 2.3 milliamperes. The third stimulus (2.0 milliamperes) is below threshold level and does not evoke a response; it is followed 40 msec later by a larger stimulus that is above threshold level. (Reprinted from Preston and Bowers,[1] by permission.)

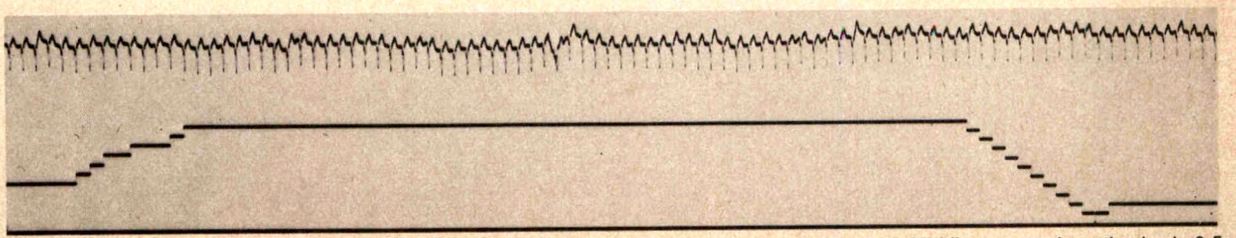

FIGURE 2. Programmed tracking mode for sensing for threshold. **Above,** electrocardiogram (5 mm/sec). **Middle,** pacemaker stimulus in 0.5 milliampere steps. **Bottom line,** 0.0 milliampere reference. **At left,** the stimulus level increases after movement of the pacing catheter to a higher threshold position. About 1 minute later (**right**) the unit automatically searches down for threshold and resets at a lower stimulus level. It is programmed to search for threshold every 2 minutes. (Reprinted from Preston and Bowers,[1] by permission.)

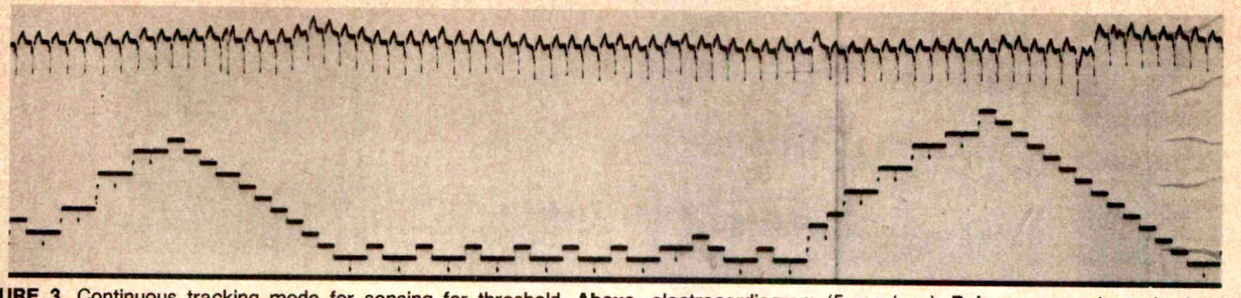

FIGURE 3. Continuous tracking mode for sensing for threshold. **Above,** electrocardiogram (5 mm/sec). **Below,** pacemaker stimulus level. Marked sudden inspiration results in catheter movement and rise in threshold. The pacemaker tracks to the higher level without missing a beat.

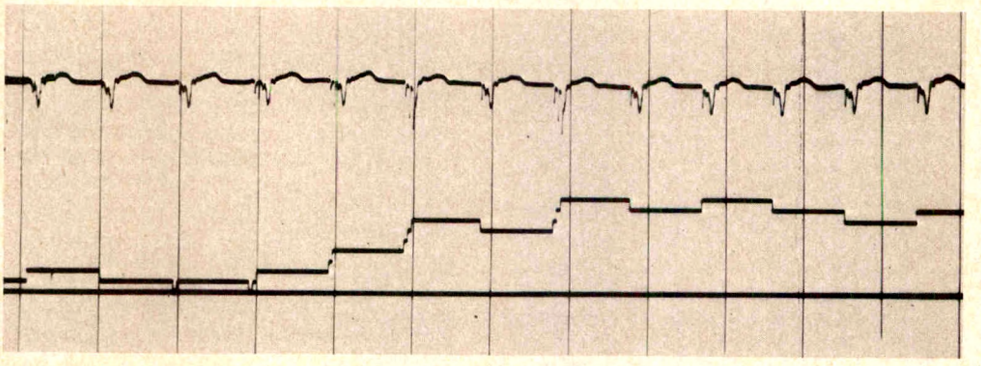

FIGURE 4. Pacemaker in continuous tracking mode. **Above,** electrocardiogram (5 mm/sec). **Below,** pacemaker stimulus level in 0.5 milliampere steps. The base line is 0.0 milliamperes. **At left,** threshold is between 0.0 and 0.5 milliamperes, and the pacemaker continuously tracks between 0.0 and 1.0 milliamperes. After the third beat the catheter was suddenly withdrawn 2 cm, resulting in a rise in threshold. The pacemaker then tracked to a higher output level, sometimes using two backup pulses (fourth, fifth, sixth and eighth beats).

ventricular beats of spontaneous or pacemaker-induced origin and of detecting the absence of ventricular depolarization after delivery of subthreshold stimuli. The pacemaker correctly responded to subthreshold stimuli by increasing the output amplitude of backup pulses. It performed as expected in the two modes of operation, continuous and programmed. When threshold changes were induced by sudden deep respiration or coughing, changes in patient position or manipulation of the catheter, the pacemaker automatically adjusted output amplitude to the new threshold level (Fig. 3 and 4). Only by manually changing the position of the pacing catheter tip were we able to produce a change in threshold great enough to require two backup pulses. The pacemaker tracked threshold elevations rapidly enough to maintain pacing except when the catheter tip was suddenly jerked backward from a low to a high threshold position. In this latter circumstance, one paced beat was missed (the regular stimulus and two backup stimuli were subthreshold), but the unit recovered to capture the next beat.

Discussion

Clinical testing of the threshold tracking pacemaker indicated its effectiveness and safety in patients requiring temporary pacing for acute medical problems. The reliability of the system must be determined by further long-term testing, but these first tests demonstrate its feasibility. Reliability is most directly a function of adequate sensing of spontaneous or pacemaker-induced beats, and the reliability of sensing is determined by the electrode system. The system contains safeguards to transform the pacemaker to the asynchronous mode in the absence of adequate sensing, so that a sensing failure would have the same result as with an ordinary noncompetitive (demand) pacemaker. In clinical testing we attempted to produce sensing failures by sudden movements of the patient or the pacing catheter but, except when the electrode was removed from the right ventricle, sensing was always adequate. Electromagnetic interference and interference from myopotentials did not occur, but the system has not been thoroughly tested for these problems. In all instances the threshold tracking pacemaker performed as a noncompetitive pacemaker and was properly inhibited by all spontaneous (nonpacemaker-induced) beats.

Advantages: The advantages of the threshold tracking pacemaker are: (1) Pacemaker output is kept in an optimal range above excitation threshold but well below fibrillation threshold; (2) the system automatically adjusts for threshold changes without missed beats or alteration in rate; (3) the system aids in electrode positioning by automatically displaying threshold level; (4) catheter or electrode stability can be monitored continuously and long-term histograms can be recorded to document threshold changes in the long-term operation of the pacing system; and (5) the system is useful in evaluating acute threshold changes secondary to activity or position of the pa-

tient or to drug therapy. Ultimately, the threshold tracking pacemaker will be incorporated into implantable units, which may increase pacemaker life by tailoring pacemaker output to beat by beat requirements. As more data are collected with regard to the requirements and potential of this unit, changes will probably occur in stimulus output.

Requirements of sensing system: The only type of pacemaker that can optimally match output against threshold and remain safe is one that will frequently and automatically test for threshold level and deliver a stimulus that is always suprathreshold but no more above threshold than is necessary to ensure effective pacing. At the Fourth International Symposium on Cardiac Pacing,[3] two automatic threshold sensing systems were reported[4,5] and a third[6] was demonstrated. Subsequently, a fourth system was reported.[7]

The essential feature of the threshold tracking pacemaker is its ability to sense for the presence or absence of ventricular depolarization after a pacing stimulus. To determine whether or not each pacemaker stimulus evoked a ventricular response the pacemaker must detect an electrical signal (QRS complex) during the 100 msec period after each stimulus. This is technically exceedingly difficult and is the limiting factor in any threshold tracking pacemaker. Ordinary noncompetitive (demand) pacemakers have a sensing refractory period of 250 to 350 msec after each delivered stimulus. This period occurs because 250 to 350 msec elapse before the afterpotential, which may be as great as 1 volt after the pacemaker stimulus, is dissipated to a level that will permit the pacemaker to sense reliably a 2 to 3 millivolt intracardiac depolarization. Reliable sensing during the 100 msec interval after the pacer stimulus requires stabilization of the electrode afterpotential in order to detect the depolarization signal.

Backup pulses to ensure continuous pacing: The pacemaker developed by Mugica et al.[4] has four output levels. In this unit an external magnet is used to trigger the pacemaker to search lower output levels for threshold, and a subthreshold stimulus is always followed by a missed beat. The system developed by Funke[6] has a greater number of output levels but also misses one ventricular depolarization every time the output falls below threshold level.

We believe that it is important to have backup pulses following subthreshold stimuli so as to avoid missing a heartbeat. When the suprathreshold backup pulse is delivered 40 to 50 msec after the subthreshold stimulus, the delay of 40 to 50 msec is sufficiently short so that there is no effective change in the heart rate (Fig. 1). Similarly, the beat to beat interval following a backup pulse is shortened by 40 to 50 msec compared with the basic pacing rate, but this change is not perceptible to the patient. The unit determines threshold by reduction of stimulus levels, but backup pulses ensure continued pacing without missing a beat and with an imperceptible change in cardiac rate. The unit was designed with a limit of two backup pulses to avoid any possibility of stimulation during the vulnerable period of a pacemaker-induced depolarization that was not sensed. A first backup pulse is delivered 40 msec after the basic stimulus and, if necessary, a second backup pulse is delivered 80 msec after the basic stimulus. If the basic driving stimulus does evoke a ventricular depolarization that is not properly sensed (worst case), a second backup pulse 80 msec later would still be too early to fall during the vulnerable period of ventricular repolarization. However, stimuli occurring in the period beginning 120 msec after the basic stimulus could fall in the vulnerable period of an unsensed depolarization after the basic stimulus. For this reason we limited the pacemaker to two backup pulses and believe that all backup pulses must occur within 100 msec of the basic stimulus. A backup pulse later than 100 msec after the basic stimulus would also cause a great enough change in the ventricular beat to beat interval to be perceived as a rate change by some patients.

The possibility of a dropped (nonpaced) ventricular beat is minimal with the threshold tracking pacemaker. A sudden change of the pacing electrode to a higher threshold position can result in a missed beat, but we found that ordinary physiologic alterations, such as deep breathing and changes in body position, produced threshold elevations of low enough magnitude to permit the pacer to track upward without missing a beat. Only by sudden withdrawal of the pacing catheter were we able to produce an instant rise in threshold so great that the pacemaker could not compensate without missing a beat. Sudden marked catheter movement does occasionally occur in clinical practice, as with "catheter displacement," and is often associated with loss of pacing. In cases of "catheter displacement" without loss of pacing, there may well be one or more missed beats at the time of catheter movement. We do not consider that the possibility of one missed beat during catheter movement is a serious limitation of the threshold tracking pacemaker.

Variations in threshold and optimal pacemaker stimulus: Since implantable pacemakers first became commercially available, recognition of factors that determine threshold has led to design of electrodes with lower thresholds. This has allowed the use of lower stimulus levels, but there is evidence that with lower threshold electrodes the percent change from acute to chronic threshold is greater than with electrodes that have higher acute thresholds.[8] Thus, the pacemaker manufacturer is still faced with designing pacemakers to match thresholds that range over a wide span. With some of the newer electrodes threshold at the time of implantation is often lower than 0.1 milliamperes,[9] whereas other long-term electrode thresholds uncommonly reach as high as 10 milliamperes (pulse duration 0.5 to 1.0 msec), producing a wide range of clinically encountered thresholds with the maximal level ranging up to 100 times the minimal level.

The necessity of providing a stimulus above threshold level is obvious. Were there no detrimental

or disadvantageous effects of pacing at very high stimulus levels, setting the stimulus at 20 milliamperes (1.0 msec) would ensure pacing in all but exceedingly rare cases. However, the optimal pacemaker stimulus level is a *threshold* stimulus, that is, a stimulus of the minimal level producing a propagated cardiac depolarization. To the extent that the stimulus exceeds the threshold level there is (1) unnecessary current drain from the battery, (2) an increased risk of pacemaker-induced ventricular fibrillation, and (3) a possible increase in tissue reaction or electrode damage, or both. The problem of pacemaker-induced ventricular arrhythmias is probably minimal, but is a potential complication of ventricular pacing.[10] Any noncompetitive (demand) pacer can malfunction and deliver stimuli during the ventricular vulnerable period. Spear et al.[11] demonstrated in dogs that the greater the current intensity delivered during the vulnerable period, the greater is the temporal dispersion in recovery of excitability, associated with a decrease in ventricular fibrillation threshold immediately after the application of current. They concluded that "since the intensity of the current delivered to the myocardium does influence vulnerability, pacemaker current output should be of as low intensity as possible to minimize these effects." The concept of the threshold tracking pacemaker is concordant with this physiologic premise.

In the future, the concept of immediate automatic monitoring of the result of an applied stimulus may be an impetus to further advances in medical technology.

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Tricuspid Atresia: Clinical Course in 101 Patients

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The clinical profile and course of 101 patients with tricuspid atresia seen at the Children's Hospital Medical Center, Boston, were reviewed; the electrocardiograms, hemodynamic data, associated anomalies, complications of the malformation and surgical results were outlined and a definition of anatomic types and radiologic groups formed in order to facilitate therapeutic decisions. Overall survival to 15 years of age was approximately 50 percent. Tricuspid atresia type I (normally related great arteries), group A (decreased pulmonary vascularity) was the most frequent category (54 percent); without surgery, these patients had only a 10 percent chance of survival beyond the 1st year of life. Surgical intervention improved chance of survival to 15 years of age to 50 percent. Overall surgical mortality was 23 percent. The Waterston shunt is the procedure of choice in symptomatic small infants with diminished pulmonary flow (group A). Type II patients with increased pulmonary blood flow (group B) would benefit from a pulmonary arterial band. In contrast, patients with group B, type I atresia would rarely need a pulmonary arterial band. Patients with spontaneously changing hemodynamics (group C) usually require a shunt later in life than those in group A, with more favorable operative results. Our experience indicates the continued need of early surgical palliation. New surgical approaches, such as the right atrial-pulmonary arterial anastomosis, may result in a more prolonged survival.

Tricuspid atresia may be defined as congenital complete absence of the right-sided atrioventricular valve, with hypoplasia of the right ventricle. It accounts for approximately 1 to 3 percent of all congenital heart defects.[1,2] Diagnostic features of this entity have been well described[3–8] and, since 1945, surgical intervention, when appropriate, has been employed to improve pulmonary blood flow.[9] Without palliative surgery prospects for long-term survival are poor, especially in the group with diminished pulmonary blood flow.[10] Shunt operations increase longevity, but to what extent is unknown.[9,11,12] Recent developments in the surgical management of tricuspid atresia[13–17] suggest a need for a review of past experience. This report, therefore, describes the clinical course of 101 patients with tricuspid atresia seen in the past 32 years at The Children's Hospital Medical Center, Boston.

Material and Methods

The hospital charts were reviewed of 101 patients with tricuspid atresia examined at the Children's Hospital Medical Center between January 1, 1941 and September 30, 1973. The diagnosis in each case was confirmed by findings at cardiac catheterization, angiocardiography or surgery or by autopsy findings, or both. This report concentrates on the electrocardiographic and hemodynamic findings and on the long-term course, including operation, complications and survival. Details of history, physical examination and clinical laboratory data have been well described and will not be repeated.[3–5]

From the Department of Cardiology, The Children's Hospital Medical Center and the Department of Pediatrics, Harvard Medical School, Boston, Mass. This study was supported in part by Grant HL05855-06 and HL09476-09 from the National Institutes of Health, Bethesda, Md. and Project 260, Maternal and Child Health Service, Health Service Administration of the U. S. Public Health Service, Department of Health, Education, and Welfare. Manuscript accepted January 29, 1975.

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TABLE I

Anatomic Classification of Tricuspid Atresia (101 patients)

Type	Patients (no.)	%	Keith* (%)
I	71	70	69
II	23	23	27
III	7	7	3
Total	101	100	99

* Anatomic classification is abbreviated from Keith et al.,[21] p 648.

Type I = normally related great arteries; Type II = *d*-transposition of the great arteries; Type III = *l*-transposition of the great arteries.

TABLE II

Anatomic Type of Tricuspid Atresia Related to Radiologic Classification (101 patients)

Type	Group A	Group B	Group C	Total
I	54	6	11	71
II	7	14	2	23
III	2	3	2	7
Total	63	23	15	101

Group A = decreased pulmonary vascularity; Group B = normal or increased pulmonary vascularity; Group C = changing pulmonary vascularity; other abbreviations as in Table I.

Ninety-eight patients had 12 lead electrocardiograms; these were examined for (1) QRS frontal plane axis (to the nearest 5°) and (2) amplitude of the P wave in lead II. All 101 patients had chest radiographs. The original interpretations of the chest films by members of the radiology staff were used in this study. Thirty-eight films that were interpreted to have increased pulmonary vasculature were reviewed by one of us (M.D.).

Ninety-five cardiac catheterizations were performed in 77 patients, of whom 29 were studied at least twice. The median age at the time of the initial catheterization was 6 months (range 1 day to 18 5/12 years). Pressure tracings in the right atrium, left atrium and left ventricle as well as systemic arterial oxygen saturation data were obtained in 63 patients. Since the pulmonary artery was rarely entered and oxygen consumption infrequently measured, the pulmonary arterial pressure and pulmonary blood flow could not be accurately assessed. There were 55 diagnostic angiograms; 28 were reviewed by one of us (M.D.) The original official interpretation of the radiology and cardiology departments was accepted in the remaining 27 cases.

Autopsy material was surveyed for (1) identification of valve atresia, (2) relation of the great arteries, (3) determination of segmental relations,[18] and (4) type and maximal dimension of the interatrial communication.

Survival curves were constructed from life tables utilizing the abstracted survival data for all 101 patients and for the subgroups therein. Statistical analyses were carried out using Student's *t* test.

Anatomic classification: We have classified our patients on the basis of catheterization and angiographic data, surgical observations and autopsy findings according to the major anatomic types proposed by Kuhne[19] and modified first by Edwards and Burchell,[20] and later by Keith et al.[21] (Table I). Type I (normally related great arteries) characterized 71 patients, 23 patients had *d*-transposition of the great arteries (type II) and 7 had *l*-transposition of the great arteries (type III). This distribution accords with findings in Keith's collected autopsy series (Table I).[21] Attempts at further anatomic subdivision according to the sites of obstruction to pulmonary flow, although possible,[22] were not undertaken.

Radiologic classification: Astley el al.[23] classified tricuspid atresia into two groups according to the radiologic appearance; group A had decreased pulmonary vascularity, whereas group B had normal or increased pulmonary vascularity. We add a third group C, characterized by spontaneously changing hemodynamics[24–27] and identified by transition from increased to decreased pulmonary vascularity in serial radiographs. Such a classification bypasses the anatomic subgrouping, but does serve as a therapeutic guide: whether to perform a shunt operation, apply a pulmonary arterial band or do nothing.

We grouped our 101 patients into these three radiologic groups and related them to the anatomic types of Keith et al.[21] (Table II). Sixty-three patients were in group A, the majority with normally related great arteries (type I). More than 50 percent of those with increased pulmonary vascularity (group B) had *d*-transposition of the great arteries (type II). A significant number, 15, could be classified into group C, most of them with type I anatomy.

Results

Sex: Sex distribution slightly favored male patients (55 percent). This ratio is similar to that of two series[8,9] containing a total of 96 patients of whom 53 percent were male.[8,9] Our findings tended to localize this male predominance to those with types II and III anatomy.

Rate per year: Ninety-three percent of the patients have been seen since 1950 (Fig. 1), when interest in and resources for treatment of congenital heart disease at our hospital were developed. The frequency of patients with tricuspid atresia seen since 1950 was approximately 4.6 per year. Tricuspid atresia accounted for 1.7 percent of all congenital heart disease seen at this institution per year; this rate increases to approximately 3 percent per year if one considers only infants with critical congenital heart disease (undergoing cardiac catheterization or surgery or dying within the 1st year of life).[28]

Age at recognition: More than 50 percent of the patients were noted to have a cardiac abnormality (cyanosis or heart murmur) on the 1st day of life (Fig. 2). The condition of only 14 went unrecognized beyond 2 months of age, and 7 of these patients had increased pulmonary vascularity. The most frequent observation indicating heart disease was cyanosis, although almost 1 in 4 (22 of 101) patients presented with a systemic arterial saturation of 80 to 92 percent at initial catheterization.

Electrocardiograms: Frontal plane QRS axes were plotted for 98 of the 101 patients, according to anatomic type (Fig. 3); 76 percent of all patients had a superior leftward frontal plane axis (0 to −90°); only 1 patient had a superior rightward axis. Inferior

leftward frontal plane axes (0 to +90°) were encountered in only 13 percent of patients with type I anatomy, but were found in nearly 50 percent of those with type II or III anatomy.

P wave amplitude in lead II was measured in 98 patients; 70 percent of those with type I and type II anatomy had abnormal P wave amplitudes (greater than 2.5 mm in lead II), a figure slightly less than the 82 percent previously reported.[8] Abnormal P wave configuration characterized by a bipeaked wave form was noted in 10 patients (P tricuspidale).[29] There was no correlation between P_{II} amplitude and age, mean interatrial gradient, right atrial *a* wave or size of interatrial communication. However, there was reasonable correlation (no. = 62, $r = 0.48$) between P_{II} amplitude in patients with types I and II anatomy and right atrial to left atrial *a* wave gradients; this correlation was more significant (no. = 18, $r = 0.69$) when only data from patients with type II anatomy were plotted.

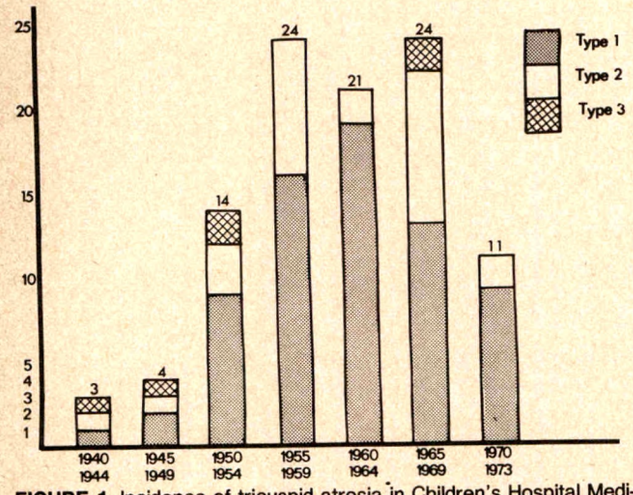

FIGURE 1. Incidence of tricuspid atresia in Children's Hospital Medical Center, Boston, 1941 to 1973, by 5 year intervals. Note the observed increase since 1950.

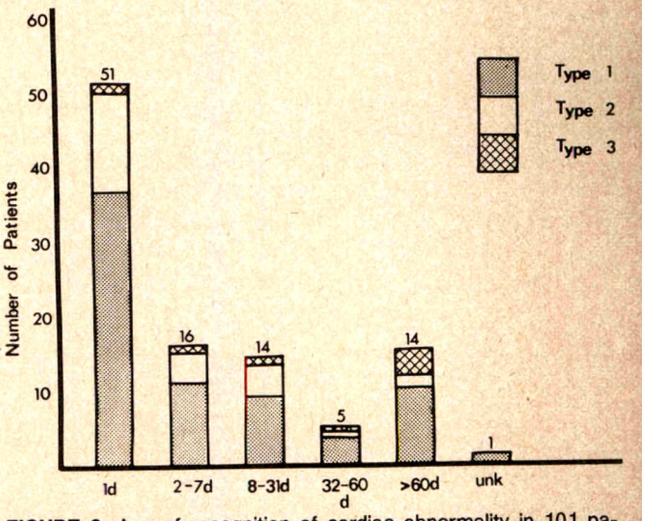

FIGURE 2. Age of recognition of cardiac abnormality in 101 patients with tricuspid atresia. d = days; unk = unknown.

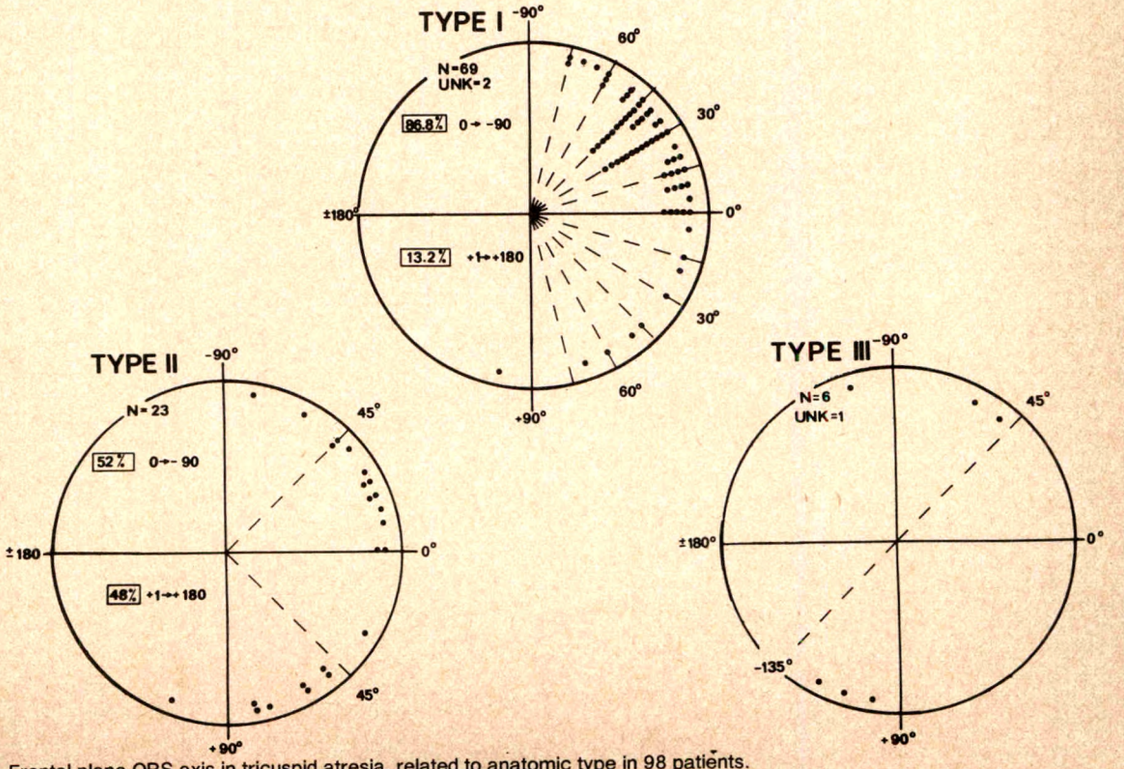

FIGURE 3. Frontal plane QRS axis in tricuspid atresia, related to anatomic type in 98 patients.

Hemodynamic data: Cardiac catheterization was performed in 77 patients. In general, the procedure was well tolerated and easily accomplished without complication. There was one death (within 24 hours of catheterization) in a newborn with severe heart failure and cyanosis (type II, group B) in 1966.

The preoperative mean systemic arterial saturation was markedly decreased in both the 34 patients in group A (58.1 percent ± 9) and the 6 patients in group C (65.8 percent ± 12); whereas in the 23 patients in group B (83.6 percent ± 9), arterial desaturation was much less apparent ($P < 0.005$).

Atrial pressures at preoperative catheterization were abnormal in 80 percent of the 63 patients studied (Table III). Right atrial pressures, both *a* wave and mean, were generally increased.[30] Although left atrial pressure levels were lower than the reported normal,[30] especially in patients in group C, there was no significant difference in the preoperative atrial pressures between patients in groups A and B; on the other hand, with the exceptions of left atrial *a* waves and right atrial-left atrial gradients, values were significantly lower ($P < 0.01$) in patients in group C.

A significant mean gradient across the atrial septum (3 mm Hg or more) at initial catheterization was present in four patients (6 percent) at ages 6 months (three patients) and 4 years (one patient). None underwent atrial septectomy or balloon septostomy. Two of these four were classified as type I, group A and both later had a Potts anastomosis with a good palliative result. The third patient (type II, group B) died without surgery at age 2 years. Extensive collateral vessels developed in the fourth patient (type III, Group A), who lived to age 22 years. Both of these latter patients had a mean interatrial gradient of 5 mm Hg and died of congestive heart failure. The 2 year old died with signs of right-sided failure related to an obstructive atrial septum. In the last 2 years of his life, the 22 year old also had signs of right-sided failure, probably exaggerated by an obstructive atrial septum. Thus, among the 77 patients who underwent cardiac catheterization for whom physiologic data are

TABLE III

Intraatrial Pressures in Tricuspid Atresia Related to Radiologic Classification (63 preoperative patients)

	Pressures (mm Hg)					
	RA*a*	LA*a*	*a* Wave Gradient	RAm	LAm	Mean Gradient
Normal*	6 ± 3.2	13 ± 3.2†	...	4.0 ± 2.6	9 ± 2.4	...
All patients (no. = 63)	12.7 ± 3.8	9.1 ± 3.6	3.3 ± 2.4	6.1 ± 2.6	5.2 ± 2.7	1.3 ± 1.3
Group A (no. = 36)	12.7 ± 3.5	8.9 ± 3.4	3.2 ± 2.2	6.3 ± 2.5	5.5 ± 2.8	1.3 ± 1.2
Group B (no. = 20)	13.9 ± 3.9	10 ± 3.9	3.6 ± 2.9	6.4 ± 2.8	5.2 ± 2.5	1.25 ± 1.26
Group C (no. = 7)	9 ± 2.6	7.8 ± 3.3	1.03 ± 0.4	4.1 ± 0.83	3.3 ± 1.1	0.79 ± 0.64

* Normal atrial pressures.[30]

† Pulmonary capillary wedge pressure.

LA*a* = left atrial *a* wave; LAm = left atrial mean pressure; RA*a* = right atrial *a* wave; RAm = right atrial mean pressure.

TABLE IV

Associated Cardiovascular Lesions (101 patients)

Type	LSVC	PDA	Coarc.	AAH	RAA	IVC to Azyg.	Asplenia	AS	Dextro-cardia	TAPVR	Tr. Art.	JAA	Total Patients
I (no. = 71)	5	2	0	0	0	0	1	0	0	1	0	0	5
II (no. = 23)	3	5	3	1	2	0	0	0	0	0	1	2	10
III (no. = 7)	0	1	0	1	0	1	1	2	2	0	0	1	5
Total (no. = 101)	8	8	3	2	2	1	2	2	2	1	1	3	20

The 35 additional anomalies occurred in 20 patients, 15 of whom had type II or type III anatomy.

AAH = aortic arch hypoplasia; AS = aortic stenosis, subaortic; Azyg. = azygous vein; Coarc. = coarctation of the aorta; IVC = absence of suprarenal inferior vena cava, drainage of inferior vena caval return by way of the azygous vein; JAA = juxtaposition of the atrial appendages; LSVC = left superior vena cava; PDA = patent ductus arteriosus; RAA = right aortic arch; TAPVR = total anomalous pulmonary venous return; Tr. Art. = truncus arteriosus.

available, only 2 had physiologic data suggesting significant obstruction by the atrial septum and died with evidence of right-sided failure; both would have benefited from decompression of the right atrium.

Congestive heart failure: Thirty-seven patients were thought to have congestive heart failure, as evidenced by cardiomegaly alone or in association with severe symptoms such as hepatomegaly, peripheral edema or pulmonary edema. Twenty-four were judged to have mild heart failure and 13 severe heart failure.

Of the 24 patients with mild heart failure, 18 had type I anatomy; heart failure developed after a shunt procedure in the nine infants in group A, whereas six in group B and three in group C had congestive heart failure without operation. Sixteen of these 18 patients are alive, ranging in age from 1 to 25 years (median 12.5 years). Four patients with type II anatomy were recognized to have mild heart failure in the 1st year of life; pulmonary arterial hypertension was documented at a later age in three, and all have survived 4 to 8 years. The final two patients with mild heart failure had type III tricuspid atresia and survived without surgical intervention into the second decade, with cardiomegaly since infancy.

Severe congestive heart failure occurred in 13 patients. Six were classified type I, group A; all had heart failure after a shunt operation, and all died within the follow-up period of this report. Three of these six died immediately postoperatively; one died 9 months later. Severe heart failure did not become manifest in two patients until the last 2 years of life; one of these died at age 17 years and one at age 20 years, both after the appearance of atrial fibrillation.

In summary, patients with mild asymptomatic congestive heart failure, identified primarily by isolated cardiomegaly, tended to maintain a stable course until at least midway into the second decade of life. In contrast, all those with symptomatic congestive heart failure died within the study period. Death occurred within 3 years of the onset of severe congestive heart failure.

Arrhythmias: Arrhythmias were noted in seven patients. Four occurred in infants at catheterization; two of these infants, both with type II, group B anomaly, were very ill. One died of ventricular fibrillation and the other was resuscitated from asystole. The other two infants (type I) had, respectively, a single brief episode of atrial fibrillation and atrial flutter; in both, reversion to normal sinus rhythm occurred spontaneously.

In the remaining three cases, atrial fibrillation had developed in older patients who had undergone shunt surgery in infancy and thus had long standing (at least 16 years) volume overload of the left ventricle. The onset of atrial fibrillation in each case exacerbated preexisting congestive heart failure.

Cardiovascular anomalies: Interatrial communications were examined in 39 autopsy specimens with tricuspid atresia. All but seven were patent foramen ovales (82 percent). Five were atrial septal defects of the secundum type, and two were ostium primum defects. The maximal diameter of the communication ranged from 0.4 to 3.3 cm.

The overall frequency of associated cardiovascular anomalies, excluding atrial defects, was 20 percent; this increased to 50 percent in 30 patients with types II and III atresia (Table IV), whereas only 7 percent (5 of 71) of patients with type I anatomy were so identified. Persistent left superior vena cava was the most common anomaly in patients with type I anatomy but also occurred in 12 percent of those with type II. Patent ductus arteriosus and coarctation of the aorta were noted especially in type II (8 of 23). Two patients with type III anatomy had subaortic stenosis that contributed significantly to their later clinical deterioration. One patient had truncus arteriosus in association with tricuspid atresia.

Bacterial endocarditis: Seven of the 101 patients had bacterial endocarditis; 2 were never clinically ill, the inactive infection being demonstrated at postmortem examination. In a third patient the diagnosis was made during an episode of documented bacterial meningitis. No detailed information is available on the fourth patient, who was not in the United States when bacterial endocarditis developed. The remaining three patients (all having had shunt procedures in infancy) had positive blood cultures and typical endocarditis, one at age 9 years and two at age 16 years.

Hypoxic spells: Episodes of hyperpnea, increased cyanosis, weakness and, occasionally, loss of consciousness occurred in 47 of the 101 patients. Only nine of these were more than 6 months old at the onset, the oldest being 2 11/12 years. Two patients died. Thirty-two of the 54 patients classified as type I, group A (60 percent) were among the 47 with hypoxic episodes as were 6 of the 14 classified as type II group B and 9 of the 11 with type I, group C atresia.

Neurologic complications: A 5 year old girl with a superior vena caval-right pulmonary arterial shunt was the only patient in whom a brain abscess developed. She was treated surgically and survived with minimal neurologic sequelae. There were three cerebrovascular accidents in our group. One was discovered at autopsy. Right hemiplegia developed in the second patient after a right Blalock-Taussig operation. The third patient (aged 8 months with a hemoglobin value of 20 g/100 ml) had hemiplegia during fever, dehydration and a profound hypoxic spell; a cerebral hemorrhage was found at autopsy. Finally two children had seizure disorders, with resting systemic arterial oxygen saturation levels of approximately 80 percent.

Surgical Results

Overall view: Patients with tricuspid atresia, particularly those in group A, are unlikely to survive beyond infancy without surgical intervention (Fig. 4). Table V presents our overall therapeutic experience related to the three radiologic groups. Overall surgical mortality was 23 percent at the first operation. Among the 48 patients in group A who were operated

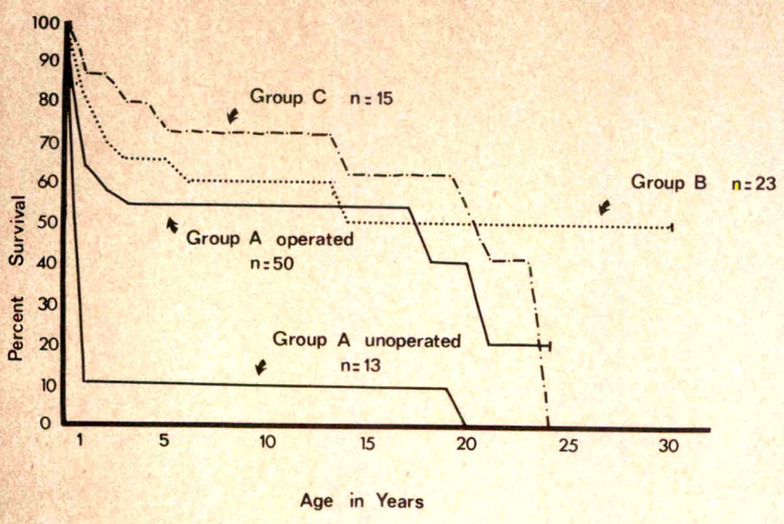

FIGURE 4. Survival curves of 101 patients with tricuspid atresia by radiologic group. Although the curves illustrating survival of postoperative patients in groups A, B and C are not significantly different, an early reduced mortality is seen in patients in group B and C. Virtually all patients in group A who did not undergo surgery died in the 1st year of life. The late mortality in all groups is related to congestive heart failure. Only two patients died at a late (interval of more than 1 year) second operation.

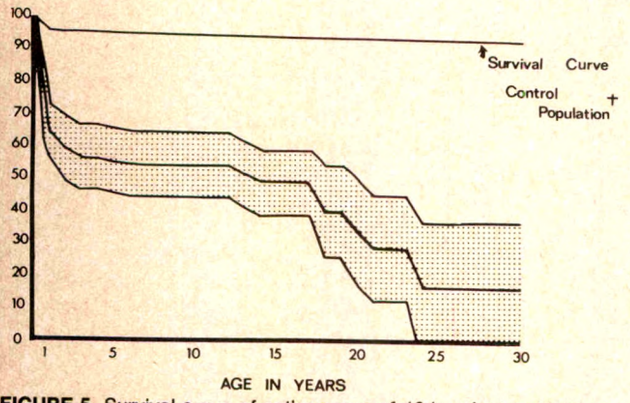

FIGURE 5. Survival curve of entire group of 101 patients with tricuspid atresia, regardless of radiologic group or treatment, with 95 percent confidence limits.

† Survival curve, females, United States, 1930–1960.[52]

on, more than 50 percent survived for 15 years, whereas only 1 of the 13 in group A who were not operated on is known to have survived infancy (Fig. 4). Only 3 of 23 patients in group B underwent surgery (two pulmonary arterial bands and one Glenn shunt) and more than 50 percent of this group, 20 of whom were treated medically, survived beyond 10 years of age (Fig. 4). All but 2 of the 15 patients in group C had a shunt performed later in life (median age at shunt creation 4 years); the mortality rate of the procedure was low. Pre- and postoperative catheterization in patients surviving a shunt operation demonstrated a 19 percent increase in the systemic arterial oxygen saturation (no. = 16, $P < 0.005$), thus confirming the improved clinical condition. One may conclude that, with appropriate management, 50 percent of the patients, regardless of their radiologic classification, survive almost to the third decade of life (Fig. 5).

Group A: decreased pulmonary vascularity: Of the 63 patients in this group only 13 were not operated on; the lone survivor was a patient with type I atresia and extensive pulmonary collateral circulation who lived for 18 years.

Fifty patients received either a systemic arterial to pulmonary arterial shunt, a superior vena caval to pulmonary arterial anastomosis or a combination thereof (Table VI); the overall mortality rate was 40 percent. The most frequently employed operation was the Waterston shunt, performed in 14 patients, of whom 5 died (Table VI). Factors influencing surgical mortality were age, weight and type of shunt performed.

Thirty-eight patients were operated on before age 1 year (Table VI). A Waterston shunt was performed in 13, of whom 4 (30 percent) died. The mechanism of death in this group varied; two patients had inadequate shunts, whereas the other two had excessive shunts with pulmonary edema. The immediate mortality of the Potts anastomosis in infants (2 of 8) was comparable, the two deaths occurring intraoperatively. By contrast all infants (less than 1 year of age, less than 10 lb) with either a Blalock-Taussig shunt or Glenn shunt as the only procedure died, except for one infant in whom the outcome is unknown. Four of the eight infants with multiple procedures died at the second operation (Table VI and VII).

Although the Potts and Waterston anastomoses resulted in a respectable salvage rate in small babies in group A, there were late complications of both palliative procedures. Six of the 10 survivors with a Potts anastomosis underwent recatheterization 9 to 16 years after operation; 4, all with the clinical suspicion of pulmonary vascular obstructive disease, had pulmonary arterial pressure in the systemic range. The remaining two had normal pulmonary arterial pressure. One patient with a Waterston shunt, also suspected of having pulmonary arterial hypertension, underwent recatheterization one month after operation; the pulmonary pressure was one-third of systemic level.

Twelve patients in group A underwent surgery at 1

TABLE V

Tricuspid Atresia: Overview of Results of Surgical Intervention by Radiologic Groups (101 patients)

	Group A (63)			Group B (23)			Group C (15)			Total (101)			
	Alive	Dead	Unk.	Alive	Dead	Unk.	Alive	Dead	Unk.	Alive	Dead	Unk.	Total
Surgery	28	20*	2	2	1	0	10	3	3	40	24	2	66
No surgery	1	11	1	9	11	0	2	0	0	12	22	1	35
Total	29	31	3	11	12	0	12	3	0	52	46	3	101

Overall mortality rate was 23 percent (19 of 66) at initial operation.
* At second operation 5 of 20 died.
Unk. = unknown; other abbreviations as in Table II.

TABLE VI

Tricuspid Atresia—Group A: Surgical Results Related to Age and Body Weight (50 patients)

Type of Procedure	<1 yr, <10 lb			>1 yr, >10 lb			Total		
	Total	Mortality	(%)	Total	Mortality	(%)	Total	Mortality	(%)
Waterston	13	4	30	1	1	. . .	14	5	36
Potts	8	2	25	2	0	0	10†	2	20
Blalock	5	4	80	0	. . .	. . .	5†	4	80
Glenn	3	3	100	5	0	0	8	3	36
ASD	1	1	. . .	0	0	0	1	1	. . .
Multiple*	8	4	50	3	1	0	11	5	45
Exploration	. . .	. . .	. . .	1	0	0	1	0	0
Total	38	18	47	12	2	17	50	20	40

* Multiple operations; mortality at second operation.
† Outcome beyond initial hospitalization is unknown in one patient.
ASD = surgical creation of an atrial septal defect.

TABLE VII

Tricuspid Atresia—Group A: Multiple Operations (11 patients)

no.	First Operation		Interval	Second Operation		Outcome	
	Type	Age		Type	Age	Alive	Dead
1	Waterston	<1 yr	4 yr	Potts	7 mo	0	1
2	R Blalock	<1 yr	2 wk	L Blalock	<1 yr	0	1
3	Blalock - Hanlon, Waterston	<1 yr	. . .	. . .	. . .	0	1
4	Glenn	<1 yr	1 day	Waterston	<1 yr	0	1
5	Blalock	<1 yr	1 1/2 yr	Potts	1 1/2 yr	0	1
6	R Blalock, ASD	<1 yr	1 10/12 yr	Potts	2 yr	1	0
7	Potts	<1 yr	4 yr	Blalock	5 yr	1	0
8	Waterston	<1 yr	4 yr	Blalock	4 yr	1	0
9	Glenn	>1 yr	10 yr	L Blalock	12 yr	1	0
10	R Blalock	>1 yr	20 yr	Band*	21 yr	1	0
11	Blalock	>1 yr	1 4/12 yr	Potts	2 yr	1	0
Total						6	5

* Survived operation, but died 3 months later.
L = left; R = right; other abbreviations as in Table VI.

year of age or older, with an operative mortality rate of 17 percent (two deaths, Table VII). Superior vena caval to right pulmonary arterial anastomosis was uniformly successful in this older age group, in contrast to the infant group. The one patient with a Waterston anastomosis died of pulmonary edema in the postoperative period. Three of these 12 operations were second procedures in patients with previously successful palliation; the one death occurred in a 2 year old boy 24 hours after a Potts anastomosis. Although surgery can be deferred beyond 1 year of age in only a minority of group A patients, surgical

TABLE VIII

Early Survival of Patients with Group B Tricuspid Atresia Related to Anatomic Type (23 patients)

Anatomic Type	Total	Survived >2 yr (no.)	Dead* (no.)	Cardiac Mortality (%)
I	6	5	1†	0
II	14	5	9‡	74
III	3	3	0§	...
Total	23	11	12	52

* Death occurred before or at age 2 years unless otherwise noted.

† Noncardiac death.

‡ Two late deaths at 17 and 28 years of age from congestive heart failure (not included).

§ Three late deaths at age 5, 12 and 13 years, respectively (not included).

TABLE IX

Management of Tricuspid Atresia, Group C, Related to Anatomic Type (15 patients)

Anatomic Type	Surgical		Nonsurgical		Total	
	no.	Alive	no.	Alive	no.	Alive
I (63)	9	7	2	0	11	7
II (23)	2	2	0	0	2	2
III (15)	2	2	0	0	2	2
Total	13	11	2	0	15	11

survival rates are apparently enhanced by this increased age.

One may conclude that in symptomatic infants with group A tricuspid atresia, a Waterston or Potts anastomosis will result in satisfactory salvage, but the patients are at risk for development of pulmonary arterial hypertension. A Glenn operation or Blalock-Taussig anastomosis is the procedure of choice for patients older than 1 year of age.

Group B: increased pulmonary vascularity: The clinical course of patients in this group depends on the anatomic type (Table VIII). All but one of the six patients with type I, a child who died from noncardiac congenital anomalies, survived without surgery. One 6 year old had, in addition, a large patent ductus arteriosus and pulmonary arterial hypertension. One patient is the oldest known survivor (29 years of age) in the entire series of 101.

In contrast only 5 of the 14 patients with type II atresia lived beyond the 2nd year of life; 4 of these have pulmonary arterial hypertension at systemic levels, 1 after receiving an ineffective pulmonary arterial band. Six of the nine deaths occurred within the 1st year of life; one occurred at operation for pulmonary arterial banding, the other five, were due to severe congestive heart failure in patients who were not operated on. The remaining three deaths occurred after the 1st year of life (at 2, 5 and 13 years of age, respectively), all as a result of congestive heart failure and pulmonary arterial hypertension (clinical).

Thus, patients with tricuspid atresia with increased pulmonary vascularity (group B) and anatomic types I or III most likely do not need palliative surgery such as creation of a shunt or pulmonary arterial banding. By contrast, most patients in group B with type II anatomy should have pulmonary arterial banding in early infancy, since pulmonary hypertension tends to develop early in this group.

Group C: changing pulmonary vascularity: Gallaher and Fyler[24] in 1967 described three nonsurgically treated patients with tricuspid atresia whose chest radiographic patterns shifted from increased to decreased pulmonary vascularity; concurrently, these patients went from a clinical state of congestive heart failure and minimal cyanosis to one of marked cyanosis, hypoxic spells and no failure. Cardiac catheterization excluded the presence of pulmonary vascular obstructive disease and demonstrated closing ventricular septal defects. In 15 of our 101 patients, the emergence of radiographically ischemic lung fields associated with decreasing arterial saturation was observed during a time course that ranged from 5 months to 18 years. Unfortunately only serial chest X-ray films and clinical observations are available in these patients.

Group C encompassed 15 patients, 13 of whom had a shunt operation with a 25 percent mortality rate (Table IX). The median age at operation was 4 years, in contrast to patients in Group A, whose median age at operation was 1 year. Among nine Blalock shunts, one Waterston and one Glenn shunt, there were no deaths. The two deaths occurred at operation in infants undergoing a Potts anastomosis. Of the 11 survivors, 5 required a second shunt at intervals that ranged from 3 months to 13 years. Thus, it appears that patients in Group C should be treated medically until progressive hypoxia requires surgical intervention.

Discussion

Clinical Features

Tricuspid atresia as an anatomic entity was recognized[31] as early as 1823; the diagnostic usefulness of the electrocardiogram is well known,[3] and has been repeatedly analyzed.[8,29,32] A superior leftward frontal plane axis, the chief diagnostic key in the electrocardiogram, was present in 76 percent of our patients, compared with its reported frequency of 81 to 82 percent.[8,29] This small discrepancy may have arisen by virtue of an increased sample size as well as inclusion of a sizable number of patients in our series with type II and type III anatomy. Although inverse correlations have been made between P_{II} amplitude and the size of the atrial septal orifice,[3,8] we, along with others,[20,29] were unable to confirm this finding. The interesting correlation between atrial *a* wave gradients and P_{II} amplitude suggests that P wave size is related to right atrial work. However, an increase in P_{II} am-

plitude as a sign of clinical deterioration[10] was not evident in our group of patients.

There were four patients (6 percent) with a significant mean gradient across the atrial septum (3 mm Hg or more) at cardiac catheterization, confirming a previously reported low incidence of interatrial mean gradient[22] and explained by the usually unobstructed patent foramen ovale.[20,33] Balloon septostomy has been recommended as a routine procedure for infants with tricuspid atresia[34] and has been used with success in cases of clear atrial septal obstruction.[35–37] Although none of our patients underwent balloon septostomy, it is likely that at least two (mean atrial gradient 5 mm Hg) would have benefited from decompression of the right atrium. It therefore appears that balloon septostomy has a role in only the few selected infants with tricuspid atresia who have an appreciable mean gradient between the right and left atrium.

Right atrial pressures, particularly in groups A and B, were increased in 80 percent of the patients not operated on. By contrast, these pressures approached normal values in group C, and thus were significantly different from values in the other two groups. The maximal right atrial pressure in our group was 25 mm Hg, present in an 18 year old with severe congestive heart failure; this is lower than the maximal pressure of 35 mm Hg previously reported.[38] Eighteen patients, 9 of whom had mild congestive heart failure, had peak right atrial pressures greater than 16 and less than 20 mm Hg, 6 after arterial shunts and 12 without shunts but with increased pulmonary vascularity (group B). In contrast, left atrial pressures were notably less than normal; they did increase in patients with severe congestive heart failure but not to statistically significant degree. We thus conclude that right atrial pressure in patients with tricuspid atresia approaches and exceeds normal left atrial pressure as the right atrium becomes the filling chamber for the systemic ventricle.

Hypoxic episodes were commonplace (47 percent), particularly in those with diminished pulmonary blood flow (group A) and normally related great arteries (type I). The mechanism of these spells in patients with type I, group A anatomy is unknown but may be similar to that postulated for patients with tetralogy of Fallot.[39] Although only two patients are known to have died during a hypoxic spell, these spells are ominous signs signaling critical diminution in pulmonary blood flow; they serve as an indication for shunt surgery in patients with pulmonary ischemia.

Bacterial endocarditis has been described in as many as 25 percent of patients surviving shunt surgery for tricuspid atresia.[9] In our experience it had a slightly lower frequency, occurring in 7 of 42 patients surviving shunt surgery (17 percent). None of our patients died of the infection.

The association of d-transposition (type II), coarctation and patent ductus arteriosus in tricuspid atresia has long been recognized[40,41] and was found in 25 percent of our patients with type II anatomy. Identification by angiogram is necessary for proper surgical management of these patients since often no significant pressure gradient can be demonstrated between the left ventricle and descending aorta. Coarctation in our group of patients was each time associated with a patent ductus arteriosus; the converse was not true. Persistent left superior vena cava, the most commonly associated cardiovascular anomaly, is of potential surgical significance in that neither a right superior vena caval-right pulmonary arterial anastomosis (Glenn) nor the Fontan operation would be practical in this setting.

Left ventricular failure, presumably as a result of increased volume load on the left ventricle by either a naturally occurring or a surgically created left to right shunt, is known to occur in tricuspid atresia[10,42] and, when severe, may lead to arrhythmias and death within 3 years.

Surgical Treatment

Surgical intervention has been mainly palliative to date and directed toward increasing pulmonary blood flow. Our overall surgical mortality rate at initial operation (23 percent) (Table V) as well as the good results in two-thirds of survivors compares favorably with reported series of arterial shunts[9,11,12] in this malformation. Although results have been related to size and age of the patients,[9,11,43] meticulous attention to anatomic detail has achieved better results in these small infants.[44]

A Potts anastomosis, effective in relieving hypoxia in this anomaly, has been documented to increase in size in growing patients from an initial 4 mm diameter to one of 17 to 20 mm[45]; such progression in orifice size appears to be related to the development of pulmonary vascular obstruction, which occurred in 4 of our 10 patients. It is unknown whether a Waterston shunt, another effective procedure for infants, also grows with the patient, and thereby also has the long-term complications of progressive pulmonary vascular obstruction. One of our 14 patients who had a Waterston shunt did demonstrate a large left to right shunt and mild pulmonary arterial hypertension. This suggests, as does our experience with Tetralogy of Fallot and Waterston shunts,[46] that the shunt does grow with the patient.

Blalock and Glenn anastomoses, ineffective in alleviating hypoxia in small infants for technical and anatomic reasons, were quite successful in older patients, and in no case did they result in elevation of pulmonary arterial pressure to systemic level. The Glenn anastomosis, in older children, has the additional advantage of avoiding an increased volume load on the left ventricle.[47] A Glenn or Blalock anastomosis thus appears to be the procedure of choice for palliation after infancy and perhaps as a second operation.

Other palliative surgical efforts included banding of the pulmonary artery for large left to right shunts, congestive heart failure and pulmonary arterial hypertension, all frequent findings in group B. Previous

reports have emphasized the increased mortality from congestive heart failure in early life in patients with type II anatomy,[26,36,48] and our experience is in agreement with the observation. Pulmonary arterial hypertension, although common in group B, type II atresia, is rare in group B, type I and has required pulmonary arterial banding in only one instance for intractable heart failure.[22,49,50] It appears, from our experience and that of others, that pulmonary arterial hypertension and congestive heart failure are infrequent early events in type I, Group B tricuspid atresia but have a high probability of occurring in type II, group B.

Development of diminished pulmonary vascularity: The mechanism of diminution of pulmonary vascularity in patients with type I, group C anatomy has been shown to be (1) closure of the ventricular septal defect[51], and (2) progressive valvular pulmonary stenosis.[15] This group was collected retrospectively over an extended period of time and included one patient with closure of the ventricular septal defect, proved at necropsy. This series also included the only four patients who did not have type I anatomy; these four patients, two with type II and two with type III anatomy, generally manifested decreasing pulmonary vascularity over a longer time course than the other patients in Group C. The number, varied anatomic type and time course of progression suggest that group C anatomy is more frequent in tricuspid atresia than previously recognized.

Surgical indications related to clinical course: Survival, as illustrated by the life table curves (Fig. 4 and 5), manifested three distinct phases. Phase I included the initial mortality of approximately 40 percent by the end of the 1st year of life, varying according to radiologic group (Fig. 4). Phase II was stable and prolonged, lasting for approximately 15 years and encompassing 50 percent of the patients. The final phase began approximately in the middle of the second decade of life, when a gradual attrition developed, attributable to congestive heart failure. There was only one surgical death, unrelated to congestive heart failure, among patients who survived beyond 10 years of age. Such a three-staged course indicates the need for early palliative surgery and suggests that perhaps earlier attempts at direct right atrial to pulmonary arterial anastomosis may be warranted, particularly as patients enter the second decade of life.

Addendum

Since acceptance of this manuscript, new information has become available regarding three patients who were initially examined during the study period (1942 to 1973). One patient, included in this study, initially presented with severe tricuspid stenosis, which developed into tricuspid atresia. Two patients not included in this report have tricuspid atresia, both are in group C, one with type II and one with type III anatomy; both have survived to the 3rd decade of life.

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Surgical Experience in Patients with Marfan's Syndrome, Ascending Aortic Aneurysm and Aortic Regurgitation

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Surgical treatment of cardiovascular complications in patients with Marfan's syndrome is usually recommended with apprehension since the systemic nature of the disease predisposes to early and late complications. To define the incidence of these complications, 30 patients were evaluated after surgical treatment of aortic insufficiency and ascending aortic aneurysm at the Texas Heart Institute. To provide a minimal follow-up period of 5 years, only patients operated upon during or before 1968 were included in this series. There were 9 female and 21 male patients aged 4 to 80 years (mean 44 years). Aortic insufficiency was treated by valvuloplasty in 3 patients and by aortic valve replacement in 27. Graft replacement of the ascending aorta was required in 23 patients, and the aneurysm was excised and the aorta repaired by direct anastomosis in 7.

Two patients were lost to follow-up study; 12 of the remaining 28 (42.8 percent) lived 5 years or more. The hospital mortality rate was 20 percent (6 of 30); the causes of death included dissection or rupture of the aorta in three patients, congestive heart failure in two and pulmonary embolism in one. The 24 survivors lived from 5 weeks to 9 years. Follow-up data were available on 22 of these patients. Ten of these (45.4 percent) died of late complications. Seven died suddenly, four of these had redissection, one patient had occlusion of the right coronary artery, and two had ventricular fibrillation of no apparent cause. The remaining three died of noncardiac causes.

Although the risk of ascending aortic and aortic valve surgery in patients with Marfan's syndrome is high, 42.8 percent of the patients in our series survived 5 years or more. We believe that surgery should be recommended for patients with Marfan's disease who have dissection of the aorta or severe aortic regurgitation, or both.

Marfan's syndrome is a generalized inherited disorder of connective tissue.[1,2] The clinical manifestations include generalized skeletal abnormalities, associated with ectopia lentis, and cardiovascular lesions, which have been reviewed in a comprehensive monograph by McKusick.[3] Although the cardiovascular complications of Marfan's syndrome are not necessarily the most disabling, they are the most frequent cause of death.[4,5]

The following comment from an editorial that appeared in 1957 seems appropriate: "In an era when slenderness and ectomorphy are being equated with long life, it may be wise to point out an exception."[6] Numerous reports have emphasized that the long-term prognosis of patients with Marfan's disease is poor because of the basic defect in connective tissue. Furthermore, recommendation for cardiovascular surgical intervention is made with a natural apprehension since the connective tissue disorder may predispose to recurrence. We report here our long-term results of surgical treatment.

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Materials and Methods

Between January 1, 1964 and December 31, 1968, 30 patients with Marfan's syndrome and aneurysm of the ascending aorta and aortic insufficiency were treated surgically at the Texas Heart Institute of St. Luke's Episcopal and Texas Children's Hospitals. Included in the series were 9 female and 21 male patients whose ages ranged from 4 to 80 years (mean 44). Only patients operated upon before or during 1968 were considered in order to provide a minimal follow-up period of 5 years. The clinical diagnosis of Marfan's disease was based upon the skeletal findings of each patient. Although some patients did not have the physical characteristics of Marfan's syndrome, all had cystic medial necrosis of the excised aorta.

The usual clinical examination was made of all patients including chest roentgenogram, electrocardiogram and routine laboratory evaluation. Of the 30 patients, 13 also underwent angiographic and cardiac catheterization studies.

Follow-up data on the 30 patients were obtained during subsequent visits to our institution or from written reports by the patients themselves or the physicians rendering primary care. The cause of death was ascertained from the hospital chart, autopsy report or the attending physician. Of the 30 patients, 2 were lost to follow-up study. These two patients were seen as outpatients up to 3 years postoperatively.

Results

Clinical features: Examination of the chest roentgenograms revealed the heart silhouette to be enlarged in all patients; there was evidence of ascending aortic aneurysm in 12. Electrocardiograms revealed left ventricular hypertrophy in 25 patients, left axis deviation with intraventricular conduction defect in 3, subendocardial ischemia in 1 and normal findings in 1. Two patients had atrial fibrillation; the other 28 had sinus rhythm.

Surgical procedure: All but seven patients underwent both replacement of the aortic valve and graft replacement of the ascending aorta (Table I). Three patients had aortic valvuloplasty and graft replacement of the ascending aorta. Valvuloplasty and primary anastomosis of the ascending aorta were not performed concomitantly in any of the patients in this series.

Survival rate: Among the total group of 30 patients, 24 survived operation and were discharged from the hospital (Table II). Length of survival in these 24 patients ranged from 5 weeks to 9 years (mean 42 months). Of the total group, 14 patients survived 3 or more years. Two of the 14 were lost to follow-up study but had been examined at the Texas Heart Institute up to 3 years postoperatively and were doing well. The remaining 12 were alive and asymptomatic 5 or more years postoperatively. The mean age of these 12 patients was 41 years.

Cause of death: Of the 16 deaths in the series, 6 (20 percent [6 of 30]) occurred within 30 days of operation (patients' mean age 51 years) and 10 more than 30 days after operation (patients' mean age 44 years) (Table III). Of the six patients who died within 30 days of operation, three had rupture of a dissecting aneurysm at a distal site, one had a large pulmonary

TABLE I

Surgical Repair in 30 Patients with Marfan's Syndrome

Procedure	Patients (no.)	
Graft	23	
Primary closure	7	
Total		30
Aortic valve replacement	27	
Valvuloplasty	3	
Total		30

TABLE II

Survival of Patients with Marfan's Syndrome Who Underwent Operation

Status	Patients (no.)
Hospital mortality	6 (20%)
Late deaths	10 (33.3%)
Late survivors (3 to 9 years)	14 (46.7%)
Total	30
5 year survival rate	12/28* (42.8%)

*Two patients were lost to follow-up but were alive and well 3 years after operation.

TABLE III

Causes of Early Death (30 Days or Less Postoperatively)

Cause of Death	Patients (no.)
Dissection	3
Congestive heart failure	2
Pulmonary embolus	1
Total	6

TABLE IV

Causes of Late Death

Cause of Death	Patients (no.)
Dissection	4
Cardiac arrest	3
Bleeding	1
Cerebrovascular accident	1
Serum hepatitis	1
Total	10

TABLE V

Annual Hospital Mortality in the 30 Patients with Marfan's Syndrome Who Underwent Operation Between 1964 and 1968

Year Operated On	Patients (no.)	Hospital Mortality
1964	5	1 of 5 (20%)
1965	11	2 of 11 (18%)
1966	4	1 of 4 (24%)
1967	8	2 of 8 (25%)
1968	2	0 of 2 . . .

embolus and two died of cardiac failure of unknown cause.

Of the 10 late deaths, 1 was associated with a cerebrovascular accident; at postmortem examination an organized clot was found around the aortic prosthesis (Table IV). One patient died from serum hepatitis, four because of additional dissection of the aorta and another because of a major hemorrhage, possibly induced by anticoagulant agents. Three other patients died suddenly; at autopsy no cause of death could be ascertained in two and the right coronary artery was occluded with a fresh thrombus in one.

Annual mortality rate: The annual surgical mortality from 1964 to 1968 is presented in Table V. It is apparent that the number of patients is too small for conclusions to be drawn concerning mortality and morbidity associated with Marfan's syndrome during those early years of open heart surgery. The period under study ended in December 1968. Since then, an additional 109 patients have undergone aortic valve replacement and repair of an ascending aortic aneurysm (some of whom had Marfan's syndrome). During the latter period, 1969 to 1973, the overall hospital mortality rate was 13 percent (14 of 109).

Discussion

The clinical manifestations and complications of patients with Marfan's syndrome are related to the basic connective tissue disorder. As a cause of death, the cardiovascular complications far exceed all others. They are estimated to occur in 30 to 60 percent of patients with Marfan's syndrome.[4] However, Murdoch et al.,[5] reported that 93 percent of 257 patients had cardiovascular lesions.

Dimond et al.,[7] in 1957, and others[8,9] have made unsuccessful attempts to arrest aortic regurgitation in these patients with the Hufnagel valve. In 1962 Conklin et al.[10] described successful palliation in a 10 year old child with Marfan's syndrome and aortic regurgitation with use of a Hufnagel valve implanted in the descending thoracic aorta. Muller et al.[11] reported successful replacement of an aneurysm with a prosthetic graft and "bicuspidation" of the aortic valve in three cases of Marfan's disease. Others[12–18] have reported 12 similar cases treated surgically. Recently, Symbas et al.[19] described one case and reviewed others previously reported. The findings from the latter report were limited, and further clinical investigation and surgical experience are necessary to determine whether the basic connective tissue defect precludes successful long-term medical or surgical results.

The survival for 5 years or more of 12 of 28 patients (42.8 percent) in our series serves to emphasize that the natural history of Marfan's disease, after surgical treatment of an ascending aortic aneurysm and aortic insufficiency, is not one of inevitable development in rapid sequence of new arterial dissection or complication.

The main cause of postoperative death appears to be related to the basic connective tissue disorder. Hemorrhage or rupture of the aortic suture lines, or both, appeared to result from a loss of tensile strength of the aorta. Aortic regurgitation persisted in some cases as a result of incomplete correction with aortic valvuloplasty, and recurred in others because of secondary, partial dehiscence of the inserted valve.

Therapeutic implications: Improved techniques of extracorporeal circulation allowing more meticulous surgical reconstruction, development of more dependable aortic prostheses, demonstration of the extent of dissection by angiography and the use of nonporous woven Dacron® grafts to establish aortic continuity all have contributed to reducing surgical mortality.[20] Although surgical treatment of the life-threatening cardiovascular complications of Marfan's syndrome is associated with high risk, the results make evident that these are not hopeless cases. The 5 year survival rate of 42.8 percent supports our belief that surgical treatment should not be withheld even though these patients have a basic biochemical defect in connective tissue that may result in future catastrophic complications.

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Coronary Artery Bypass in Patients Over 70 Years of Age: Indications and Results

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With recent advances in all phases of coronary care and the increasing success of coronary arterial surgery, operative treatment of coronary artery disease is more readily recommended, even for patients over 70 years of age. In a series of 3,730 patients who underwent aortocoronary bypass from November 1969 through June 1974, there were 95 patients who were 70 years of age or older. The primary indication for surgery was severe angina, which was present in 88 patients. The mean coronary arterial score was 9.51. Associated valvular lesions were treated surgically in 21 patients, and a left ventricular aneurysm was resected in 7. Improvements in surgical technique and postoperative care are responsible for the hospital mortality rate of only 4.8 percent in the 21 patients operated upon during the first 6 months of 1974 compared with the overall mortality rate of 22.1 percent in all 95 patients. Long-term follow-up among the 95 patients includes data from 33 patients: 9 patients whose condition improved, 21 who were asymptomatic and 1 "coronary death".

Surgical treatment of noncardiac atherosclerotic lesions is now performed routinely in patients of all ages, including those in their seventh and eighth decades. Recent advances in all phases of coronary care have greatly reduced the risk of coronary artery bypass procedures,[1–4] and surgical treatment of coronary arterial occlusive disease is now recommended without apprehension, even for patients over 70 years of age. We present our experience with patients in this age group who underwent aortocoronary saphenous vein bypass surgery at the Texas Heart Institute from 1969 through the first 6 months of 1974.

Clinical Material

Among 3,730 patients who underwent surgical treatment of occlusive coronary artery disease, 95 were 70 years of age or older. There were 75 men and 20 women whose ages ranged from 70 to 79 years (average 71.9 years).

The outstanding symptom noted on admission to the hospital was angina pectoris (88 patients, 93 percent); in 52 it was of the crescendo type and in 17 it was classified as preinfarction angina. Ten patients were considered to be in functional class II, 62 in class III and 23 in class IV (New York Heart Association classification). Eleven patients had congestive heart failure at the time of admission. A history of one or several previous myocardial infarctions was reported by 49 patients, and 55 had electrocardiographic evidence of an old myocardial infarction (27 anterolateral and 28 posteroinferior). Three women and 11 men had diabetes mellitus, and 20 patients had been treated for hypertension. Seventeen patients had symptoms of associated peripheral atherosclerotic vascular disease.

Selective coronary arteriography was performed in all patients and revealed single vessel disease in 9, double vessel disease in 22, triple vessel involvement in 50 and quadruple vessel disease, including a lesion in the left main coronary artery in 14 patients. The mean coronary arterial score, according to the method of Friesinger et al.,[5] was 9.51 (Table I). The mean left

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TABLE I

Symptoms and Preoperative Characteristics in 95 Patients 70 Years of Age or Older Who Underwent Aortocoronary Bypass Surgery

Year	Patients (no.)	Angina	NYHA Functional Classification III	NYHA Functional Classification IV	Previous Myocardial Infarction	CHF	Mean Coronary Arterial Score	Associated Anomalies: Valvular Lesions	Associated Anomalies: Left Ventricular Aneurysm	Associated Anomalies: Ascending Aortic Aneurysm
1969	1	1	1	...	...	...	4.00	1	...	...
1970	2	2	...	1	2	1	9.00	...	1	...
1971	23	22	17	5	16	2	9.35	7	3	...
1972	17	17	13	2	11	2	9.12	3	1	...
1973	31	27	18	11	14	4	10.16	11	2	...
1974 (Jan-June)	21	19	13	4	12	2	8.59	4	...	1
Total	95	88	62	23	55	11	9.51	26	7	1

CHF = congestive heart failure; NYHA = New York Heart Association.

TABLE II

Operative Procedures and Methods

Year	Patients (no.)	Graft: Single	Graft: Double	Graft: Triple	Graft: Quadruple	Endarterectomy	AVR	MVR	Resect Left Ventricular Aneurysm	Resect Ascending Aortic Aneurysm	Hypothermia	Mean Total Ischemic Time (min)
1969	1	1	...	...	...	...	1	...	...	...	...	25.0
1970	2	1	1	...	...	...	...	...	1	...	...	53.5
1971	23	6	14	3	...	9	5	...	2	...	2	42.2
1972	17	5	6	6	...	3	2	...	1	...	8	50.5
1973	31	6	10	14	1	4	7	2	2	...	27	57.0
1974 (Jan-June)	21	3	6	9	3	4	4	...	...	1	18	55.6
Total	95	22	37	32	4	20	19	2	6	1	55	51.6

AVR = aortic valve replacement; MVR = mitral valve replacement.

ventricular end-diastolic pressure was 15.03 mm Hg. A left ventricular angiogram revealed an aneurysm in 7 patients and a pronounced hypokinetic or akinetic area of the left ventricular wall in 23. Associated anomalies included severe aortic valve stenosis in 17 patients, aortic insufficiency in 4, mitral insufficiency in 4 and idiopathic hypertrophic subaortic stenosis in 1. Concomitant procedures included resection of an ascending aortic aneurysm in one patient and of an abdominal aortic aneurysm in three patients, repair of a hiatal hernia in four and a cholecystectomy in two patients.

Operative Technique

All patients underwent aortocoronary artery bypass surgery with use of a reversed saphenous vein and total cardiopulmonary bypass. Priming was accomplished with 30 ml/kg body weight of 5 percent dextrose in Ringer's lactate solution. Flow rates from 40 to 55 ml/kg with a bubble oxygenator were used, maintaining a mean arterial pressure of at least 50 mm Hg. A left atrial vent was inserted through the right superior pulmonary vein. Moderate general hypothermia was achieved by core cooling to 30° C, and the heart was cooled topically with saline solution cooled to 12° C in 55 patients, a routine procedure since 1973. Anoxic cardiac arrest was induced in all patients by cross-clamping the aorta. Until 1973 this procedure was carried out as one total cross-clamping period; since then, intermittent aortic occlusion has been used during performance of the distal anastomosis and partial occlusion of the ascending aorta for the proximal anastomosis.

The mean total ischemic time was 52 minutes for all patients (Table II). A single graft procedure was performed in 22 patients, a double in 37, and a triple in 32; a quadruple bypass graft was placed in 4. It was necessary to perform endarterectomy of the right coronary artery in 16 patients, of the left anterior descending artery in 3 and of the obtuse marginal branch of the circumflex artery in 1 patient. Concomitant aortic valve replacement was performed in 19 patients, 15 of whom received a single aortocoronary vein graft. Of four patients who had mitral insufficiency, two underwent mitral valve replacement.

Results

Operative mortality: Of the 95 patients, 16 died in the immediate postoperative period. Thirteen patients died from myocardial failure—either when

TABLE III

Nonfatal Complications and Early Postoperative Mortality

Year	Patients (no.)	Low Cardiac Output	Arrhythmia	Subendocardial Ischemia	New Myocardial Infarction	Postop Bleeding	Pulmonary Complications	Overall Early Mortality (30 days postop)	1st Day Mortality: Myocardial Insufficiency	1st Day Mortality: Arrhythmia
1969	1	...	...	...	...	...	...	1	1	...
1970	2	...	1	1	...	1	...	1	1	...
1971	23	...	9	2	2	1	2	6	3	...
1972	17	...	4	...	1	...	1	3	1	2
1973	31	4	9	6	2	1	...	9	6	1
1974 (Jan-June)	21	4	6	2	1	...	2	1	1	...
Total	95	8	29	11	6	3	5	21	13	3

Postop = postoperative.

coming off cardiopulmonary bypass (11 patients) or during the first 24 hours after operation (2 patients). Three patients died on the first postoperative day from sudden, irreversible ventricular fibrillation that occurred after a new myocardial infarction in one and had no apparent cause in two. One patient died after 21 days from acute left ventricular infarction and one died 14 days postoperatively from multiple causes, including cerebral emboli and pulmonary infection. The early myocardial mortality rate was therefore 19 percent (18 patients). Three other hospital deaths occurred, two from massive gastrointestinal hemorrhage because of stress ulcerations after 9 and 25 days, respectively, and one from pulmonary complications after 14 days. The overall hospital mortality rate was therefore 22.1 percent (21 patients). Of these 21 patients, 9 had associated cardiac operations; 7 underwent valve replacement and 2 resection of a left ventricular aneurysm, thereby reducing the mortality rate for coronary arterial surgery alone to 12.6 percent.

Operative complications: Nonfatal postoperative complications (Table III) included low cardiac output in 8 patients requiring temporary treatment with vasopressor agents, the appearance of a new myocardial infarction (new Q wave) in 6 patients and electrocardiographic evidence of subendocardial ischemia (S-T segment depression) in 11 patients. Nonfatal transitory arrhythmias included atrial fibrillation in 12 patients, atrial flutter in 3, premature ventricular contractions in 8 and premature atrial contractions in 6. Postoperative bleeding necessitating a second thoracotomy occurred in only three patients.

At present, 33 patients are included in the late follow-up study, and the mean follow-up period is 1.6 years. One patient was operated upon at the end-stage of coronary artery disease after having had five myocardial infarctions; he became asymptomatic but died from congestive heart failure 20 months postoperatively. Another patient died after 2 months from severe aortic insufficiency due to a periprosthetic leak caused by acute bacterial endocarditis after aortic valve replacement. One other patient died 1 year after operation from metastatic carcinoma of the parotid gland. After surgery, 21 patients were free of angina, 9 experienced some relief and the condition of 2 was unchanged.

Discussion

Since surgical procedures carry a higher risk in patients 70 years of age or older,[1,3] the indication for major surgical intervention in this age group depends to a great degree on the quality of life desired by the individual patient. The main goals of myocardial revascularization are to relieve severe and often disabling chest pain and to help the patient maintain or improve the vitality of his life. When medical treatment alone fails to accomplish these two aims, patients, even in older age groups, should have the benefit of surgical treatment.

In recent reports[2–4] the mortality rates for patients in their seventh decade who underwent coronary arterial surgery, although not prohibitive, were higher than for younger patients. This was true in our series in which the operative mortality rate of 22 percent in the older age group compared unfavorably with the overall mortality rate of 6.4 percent in patients of all ages. Ashor et al.[3] reported a total mortality rate of 10 percent among 100 patients 65 years of age or older who underwent coronary arterial surgery; however, the mortality rate was 18.22 percent in patients who were 70 years or older in this same series. In our series 23 percent of the patients also had associated cardiac valve replacement compared with only 3 percent of the patients in their report.

Factors leading to reduced surgical mortality: Although there was no significant difference in the severity of symptoms and coronary lesions in older patients operated upon during any single year since 1969 (Table I), there was a striking reduction in the postoperative mortality during the first 6 months of 1974 (Table III). Among 21 patients 70 years of age or older who had coronary bypass surgery between January and June 1974, only one early postoperative

death occurred. Technical advances responsible for this improved survival rate include better myocardial protection from prolonged ischemia through intermittent myocardial perfusion by an aortic cross-clamp release between the different distal anastomoses in all 21 patients and the use of a partial occluding clamp on the aorta for performance of the proximal anastomosis in 6 patients. To reduce subendocardial damage due to prolonged ventricular fibrillation during the period of anoxic cardiac arrest, small doses of propranolol hydrochloride (Inderal®) were administered before cross-clamping of the aorta of all patients who had left ventricular hypertrophy due mainly to aortic valve stenosis.[6] Of the 21 patients, 4 had low cardiac output during the first postoperative day and recovered with careful use of vasopressor agents. Dopamine hydrochloride is now being used in some of these older patients, replacing epinephrine and Levophed® (levarterenol bitartrate), and may constitute an improvement in the postoperative management of these cases.

We agree with Wisoff[7] that technical factors are very important; one is the completeness of the myocardial revascularization procedure. One patient in our series who underwent aortic valve replacement for severe aortic stenosis in addition to insertion of one aorta to right coronary artery bypass graft sustained an acute left ventricular infarction and died 21 days after operation. Preoperative coronary arteriography had shown evidence of complete occlusion of the right coronary artery and 75 percent stenosis of the circumflex branch of the left coronary artery in this patient. A second bypass to the obtuse marginal or distal circumflex branch might have prevented the death of this patient.

Indications for surgery in older age group: The optimal age at which a patient should undergo coronary surgery is still being debated.[8] Because mortality rates in all surgical reports[1,3,4] are higher for older age groups, it would appear that patients should undergo coronary arterial surgery before irreversible myocardial damage has occurred as a result of repeated myocardial infarctions.[9] More than 50 percent of the patients in our series of 95 patients had one or several myocardial infarctions before admission to our hospital. Since preinfarction angina is a widely accepted indication for surgical treatment,[6,10] more patients will be operated upon at an earlier stage of disease in future years. With achievement of a higher degree of perfection in anesthesiologic and surgical techniques and improvements in postoperative care, operative mortality can be further reduced, making coronary arterial occlusive lesions as amenable as peripheral vascular disease to surgical treatment.

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Echocardiographic Findings of Ventricular Septal Rupture in Acute Myocardial Infarction

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Echocardiograms were recorded both before and after the clinical appearance of an autopsy-confirmed interventricular septal rupture in a patient with an acute myocardial infarction. The major findings were related to the upper portion of the interventricular septum. Before rupture, this portion of the septum was relatively akinetic with a slight anterior motion during systole, whereas after rupture there was a marked increase in the amplitude of septal motion with abrupt posterior motion occurring with the onset of ventricular diastole.

When rupture of the interventricular septum complicates the course of an acute myocardial infarction invasive studies are frequently necessary to differentiate it from mitral regurgitation secondary to papillary muscle rupture.[1–5] This is particularly true when surgical intervention is contemplated. We present herein the echocardiographic findings obtained both before and after the appearance of the clinical signs of interventricular septal rupture in a patient with an acute myocardial infarction. The rupture was subsequently confirmed at postmortem examination. We believe that the data may be of value in the differential diagnosis of this catastrophic event.

Case Report

An 80 year old man was admitted to the coronary care unit with substernal aching, nausea and diaphoresis of 6 hours' duration. There was no previous history of cardiovascular disease although 4 weeks before admission digoxin therapy was started for unknown reasons.

Physical examination on admission revealed an elderly man in no acute distress. The blood pressure was 120/80 mm Hg and the pulse was 60/min with occasional ventricular extrasystoles. The skin was warm and moist. Examination of the chest revealed an increased thoracic anteroposterior diameter with scattered expiratory pulmonary wheezes. There was no evidence of jugular venous distension or peripheral edema. Examination of the heart revealed a low amplitude apical impulse in the left mid-clavicular line without a thrill, heave or paradoxical pulsation. The first and second heart sounds were of diminished intensity with a prominent fourth heart sound heard at the apex. No murmurs or rubs were heard. The electrocardiogram revealed sinus rhythm, frequent ventricular premature beats, left axis deviation and evidence of an acute diaphragmatic wall myocardial infarction.

The patient was placed on a regimen of bed rest and given morphine, nasally administered oxygen and intravenously administered lidocaine. A routine echocardiographic study was performed (Fig. 1A). Serum enzyme studies confirmed the diagnosis of acute myocardial infarction. On the 2nd hospital day the patient complained of the sudden onset of shortness of breath and right-sided pleuritic chest pain. He appeared acutely ill and dyspneic with a blood pressure of 110/60 mm Hg and a pulse rate of 110/min. For the first time a systolic thrill and a grade 3-4/6 pansystolic murmur were heard, both maximally at the lower left sternal border. A repeat echocardiographic study was performed (Fig. 1B). During the ensuing 12 hours progressive irreversible cardiogenic shock developed and the patient died on the 3rd hospital day.

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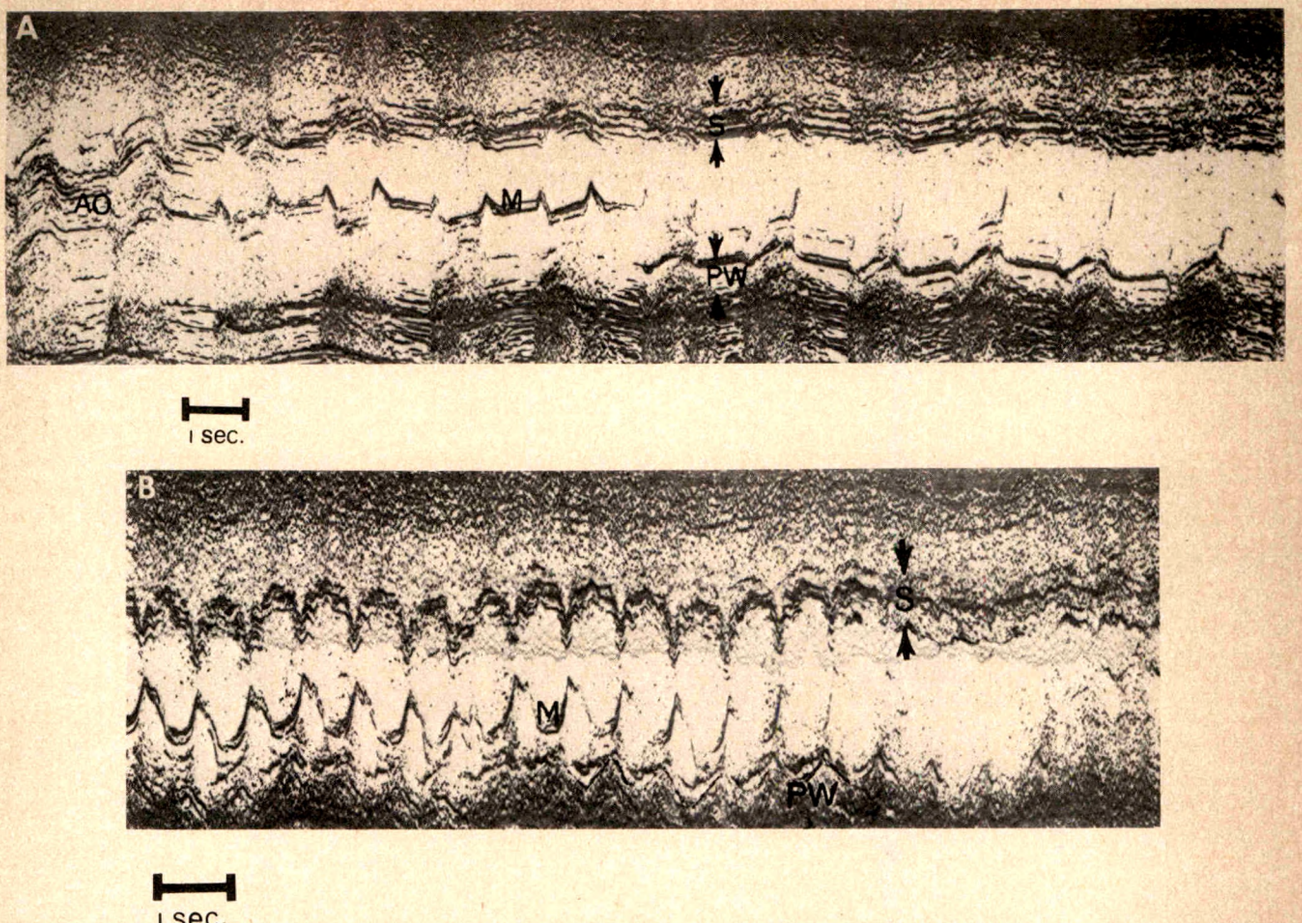

FIGURE 1. Echocardiograms. **A,** on admission, showing a scan performed from the cardiac base to the apex, moving from left to right. Note the generally decreased motion of the interventricular septum (S) with slightly anterior systolic motion in the upper portion. As one scans toward the cardiac apex, the amplitude of septal motion decreases (to the right of letter S). Ao = aortic root; M = mitral valve leaflet echo; PW = left ventricular posterior wall echo. **B,** approximately 5 hours after the appearance of clinical signs of septal rupture. The scan was performed from the base to the apex, moving from left to right. The upper portion of the septum (S) exhibits a markedly increased amplitude of motion, whereas the lower portion (to the right of S) remains relatively akinetic. M = anterior mitral valve leaflet echo; PW = general area of left ventricular posterior wall echo.

Pathologic Findings

Pertinent findings at autopsy were limited to the heart, which weighed 410 g. Sectioning revealed marked softening of the posterior portion of the interventricular septum. Approximately 1.8 cm below the posteromedial mitral leaflet a defect, which measured 1.0 by 1.5 cm, was observed in the posterior portion of the septum. A section through this area disclosed yellow mottling and thinning of the myocardium. The papillary muscles were grossly normal. Examination of the coronary arteries revealed severe atherosclerosis of all three major coronary branches with a recent thrombosis of the right coronary artery approximately 1.0 cm from its ostium.

Echocardiographic Findings

With the patient in the supine position, echocardiographic studies were performed with use of the subxiphoid approach described by Chang and Feigenbaum.[6] An Ekoline 20 ultrasonic machine (SKI Instruments, Palo Alto, Calif.) and a 2.25 megahertz, 1.25 cm diameter transducer with an unfocused beam (Aerotech Labs, Lewistown, Pa.) were used. Recordings were made on a Honeywell 1856 Visocorder.

The admission echocardiogram (Fig. 1A) exhibits an overall decrease in the amplitude of interventricular septal motion. Closer inspection reveals a slight anterior motion of the septum away from the left ventricular posterior wall during systole that tends to diminish as one scans toward the cardiac apex, the septum becoming essentially flat. Normally the interventricular septum moves posteriorly toward the left ventricular wall during systole, and its amplitude of motion increases as one scans toward the cardiac apex.[7] The anterior mitral valve leaflet echo appears normal.

Figure 1B shows the echocardiogram performed approximately 5 hours after the appearance of the clinical signs of septal rupture. The upper portion of the septum, which originally had a slight anterior displacement during systole now demonstrates a markedly increased amplitude of motion. An abrupt posterior motion with the onset of ventricular diastole is also seen. In addition, the upper portion of the septum, when compared with the lower portion, appears considerably thinner. The lower portion of the sep-

tum (to the right of the letter S in Figure 1B) is relatively akinetic, essentially unchanged from the admission tracing. The anterior mitral valve echo reflects the increase in cardiac rate from the earlier tracing, but otherwise remains normal.

Discussion

In isolated congenital ventricular septal defects, there are no specific echocardiographic findings unless the defect is quite large, whereas coronary artery disease alone has been shown to be one cause of abnormal interventricular septal motion.[7] In a series of 48 patients with documented coronary artery disease Jacobs et al.[8] found a high correlation between diminished, flat or paradoxical septal motion and significant disease of the left anterior descending coronary artery. The abnormal interventricular septal motion seen on admission in our patient (Fig. 1A) was probably due to coronary disease and recent infarction. The absence of other known causes of abnormal motion (left bundle branch block, isolated right ventricular volume overload, prosthetic aortic valve) and the postmortem findings of a large infarction involving the interventricular septum tend to support this hypothesis.

The lower portion of the interventricular septum remained relatively akinetic both before and after the clinical signs of septal rupture appeared. Although less involved in the ischemic process than the upper portion of the septum, this portion apparently was not able to resume active contraction. The major echocardiographic change after the septal rupture was observed in the upper portion of the septum. The area that had exhibited slight anterior motion during systole before rupture demonstrated, after rupture, a marked posterior motion with the onset of ventricular diastole (Fig. 1B). Two possible explanations can be considered for the change in interventricular septal motion; the first is that this represents a dynamic response of the septum to a biventricular volume overload; the second is that it represents passive motion of a flail dyskinetic septum. We favor the latter explanation since it appears to correlate well with the pathologic finding of extensive infarct in the basal portion of the septum. It would be unexpected for an extensively infarcted septum to respond dynamically to a sudden volume overload and, in addition, have the less ischemic apical portion respond little or not at all. The infarcted portion of the septum probably moved passively downward during isovolumetric relaxation and then moved anteriorly as the ventricle began to fill with blood.

Use of the subxiphoid approach in our studies may have been responsible for our ability to record these changes in septal motion, and our findings may not correlate exactly with the septal motion usually recorded from the left sternal border. Nonetheless, we believe they may be of value in differentiating ventricular septal rupture from other catastrophic events that occur in the course of an acute myocardial infarction.

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Echocardiographic Findings in Uhl's Anomaly

Demonstration of Diastolic Pulmonary Valve Opening

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The echocardiographic findings in a case of Uhl's anomaly, or congenital hypoplasia of the right ventricular myocardium, are reported. Diastolic opening of the pulmonary valve is described. Comparison is made with echocardiograms in Ebstein's disease of the tricuspid valve, and it is suggested that echocardiography can help in differentiating these two entities. In addition to the pulmonary valve finding, increased right ventricular dimension, delayed tricuspid closure and abnormality (prolapse) of the mitral valve were noted. The echocardiographic findings are compared with cardiac catheterization data.

Uhl's anomaly, or congenital hypoplasia of the right ventricular myocardium, was described in 1952.[1] In addition to the right ventricular abnormalities, more extensive involvement has been reported, including elements of endocardial fibroelastosis and myocardial hypoplasia of other cardiac chambers.[2–6] Although the anomaly is an uncommon congenital heart lesion,[1–21] it presents a difficult clinical problem since it may be confused with Ebstein's disease of the tricuspid valve, pericardial effusion or other forms of cardiomyopathy. This report describes the echocardiographic findings in a case of Uhl's anomaly, the most remarkable component being a demonstration of diastolic opening of the pulmonary valve. Comparison with reported echocardiographic findings in Ebstein's disease of the tricuspid valve suggest that the echogram may help to differentiate these entities.

Case Report

The patient was a 14 year old girl who had had a benign medical history until the age of 4 1/2 years, when she was thought to be mildly cyanotic during a routine physical examination. At age 5, right heart catheterization data and an angiocardiogram were interpreted as indicating Ebstein's anomaly of the tricuspid valve with an atrial septal defect and a small right to left shunt. From age 5 to age 13, she gradually became more cyanotic, had a loss of exercise tolerance and manifested intermittent atrioventricular (A-V) dissociation with a junctional pacemaker in periodic electrocardiograms.

On recent physical examination, there was marked cyanosis but no acute distress. There was a visible systolic impulse in the anterior axillary line at the fifth intercostal space. On auscultation, the first heart sound (S_1) was normal, the second (S_2) was widely split and fixed, with a normal pulmonary component. A third heart sound (S_3) was detected midway between the left sternal border and the cardiac apex at the level of the fourth intercostal space. No significant murmur was heard. The liver, located 5 cm below the right costal margin, was nontender and nonpulsating. There was marked clubbing of the digits.

Chest X-ray examination revealed overall cardiomegaly with a large atrial and right ventricular shadow. The pulmonary vascularity was normal. An electrocardiogram indicated first degree A-V block, P pulmonale and a pattern of right bundle branch block. The hematocrit was 67 percent.

A standard echocardiographic examination[22] revealed three cardiac chambers, four cardiac valves and two great arteries. The pulmonary valve was identified by rotating the transducer ventrally, leftward and cephalad

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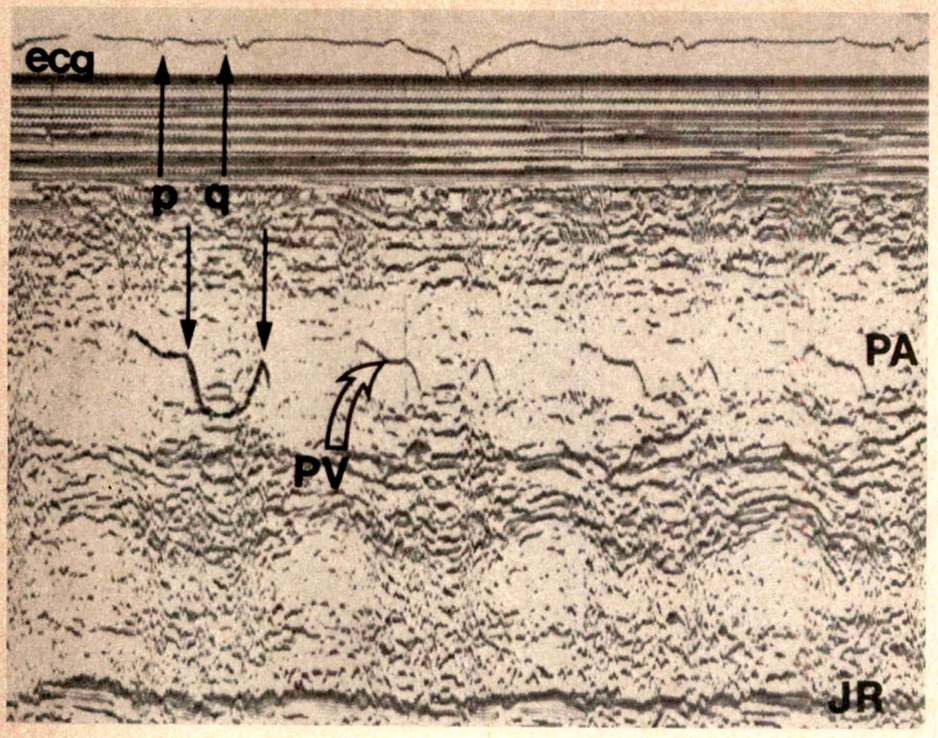

FIGURE 1. Pulmonary valve echogram showing abnormal pulmonary valve opening that occurred before ventricular depolarization (q) and coincided with atrial systole. Note that the valve opens, closes and reopens with ventricular systole. The first complex has been retouched for clarity. ecg = electrocardiogram; p = P wave; PA = pulmonary artery; PV = pulmonary valve. Unmarked **vertical arrows** indicate points of valve opening.

TABLE I

Cardiac Catheterization Data

Site	O_2 Saturation (%)	Pressure (mm Hg)
Inferior vena cava	48	
Superior vena cava	46	
Right atrium	48	a = 17, v = 15, m = 14
Right ventricle	46	17/13, ps 16
Main pulmonary artery	48	17/14, ps 16
Left atrium	58	a = 16, v = 16, m = 12
Left ventricle	63	99/15

a = a wave; m = mean; ps = presystolic wave; v = v wave.

from the position of the aortic valve leaflets. The most striking finding was the diastolic opening of the pulmonary valve, which coincided with atrial systole (Fig. 1). The valve opened with atrial systole, partially closed and opened again with the onset of ventricular systole. In addition, pansystolic prolapse of the mitral valve and tricuspid valve was identified (Fig. 2). The tricuspid valve closure was delayed 0.07 second when compared with mitral valve closure (Fig. 2). The right ventricular dimension was increased and the ventricular septal motion was considered normal.

Cardiac catheterization results are contained in Table I. Abnormal findings included increased right atrial pressure, particularly the a wave; increased right (and left) ventricular end-diastolic pressure; absence of obstruction at the pulmonary valve and a narrow pulmonary arterial pulse pressure. A large atrial septal defect with right to left shunting was documented. Figure 3 shows catheterization pressure tracings from the pulmonary artery, right ventricle and right atrium. The right atrial a wave is transmitted into the right ventricle and pulmonary artery. Angiography revealed a large adynamic right ventricle, a large right atrium and a tricuspid valve that was not displaced. The left ventricle appeared moderately enlarged and hypodynamic although to a much lesser degree than the right ventricle.

At surgery, the large right atrium, right ventricle and atrial septal defect were identified. The tricuspid valve was deformed but no abnormal displacement was noted and the right ventricular myocardium was hypoplastic. The atrial septal defect was closed and a biopsy was performed on a portion of the right ventricle, which was subsequently plicated. Biopsy revealed elements of endocardial fibroelastosis, myocardial hypoplasia and fatty infiltration consistent with Uhl's anomaly. The left ventricular chamber was not entered.

Discussion

The normal pulmonary valve echogram (Fig. 4) may have a small posterior "dip" in diastole coinciding with atrial contraction. With the onset of ventricular systole, the pulmonary leaflets fly apart giving a characteristic box-shaped configuration, although echocardiographic recording of more than one pulmonary valve leaflet (usually a posterior leaflet) is not common beyond the neonatal period. Diastolic movement of the pulmonary valve leaflet has been previously described only in significant pulmonary stenosis,[23] where the motion probably represents doming rather than opening of the leaflets.

Pathophysiology of Uhl's disease: The pulmonary echocardiographic abnormalities in this case are consistent with the unique pathophysiology in Uhl's anomaly described by Arcilla and Gasul.[4] As a result

of a noncompliant hypoplastic right ventricle and a dynamic right atrium producing an elevated contractile wave, the atrial pressure wave is transmitted through the right ventricle and to the pulmonary artery as a presystolic wave, which may be of approximately the same magnitude as the right ventricular and pulmonary arterial peak systolic pressures (Fig. 3). The presystolic wave exceeds the pulmonary arterial diastolic pressure, creating a diastolic gradient across the valve and initiating flow into the pulmonary arteries before ventricular systole. Comparison of pulmonary valve and tricuspid echograms (Fig. 1 and 2) shows clearly that the pulmonary valve opens before the tricuspid valve is closed, confirming an observation by Gasul et al.[6] Similar pressure findings have been described in Ebstein's disease of the tricuspid valve. However, the marked increase in right ventricular end-diastolic pressure is thought to be more characteristic of Uhl's anomaly.[4] This phenomenon of diastolic opening is the opposite of that seen with increased pulmonary vascular resistance or pulmonary hypertension, when both the diastolic gradient and diastolic motion at the pulmonary valve are abolished.[23,24]

Differentiation from Ebstein's disease: The clinical resemblance of Uhl's anomaly to Ebstein's disease of the tricuspid valve has been discussed by Gasul et al.[6] Differential points that favor a diagnosis of Uhl's anomaly include angiographic and anatomic

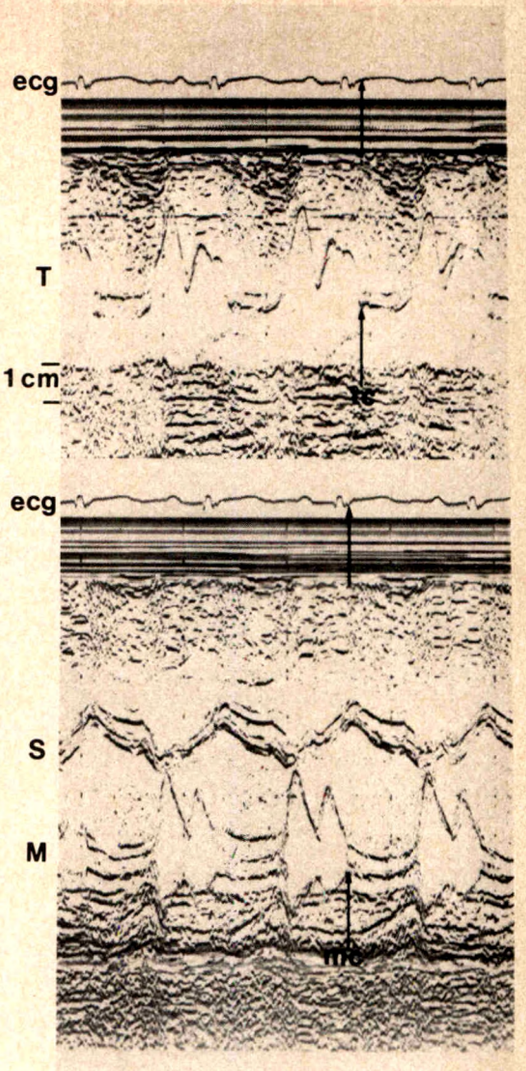

FIGURE 2. Mitral (**lower**) and tricuspid (**upper**) echograms showing tricuspid valve configuration. The **vertical arrows** indicate tricuspid and mitral valve closure. Tricuspid valve closure is delayed 0.07 second when compared with mitral valve closure. The E-F slope of both valves is greater than 100 mm/sec and the excursion is 22 mm for the mitral and 24 mm for the tricuspid valve. There is pansystolic prolapse of the mitral valve. M = mitral; mc = mitral valve closure; S = ventricular septum; T = tricuspid; tc = tricuspid valve closure.

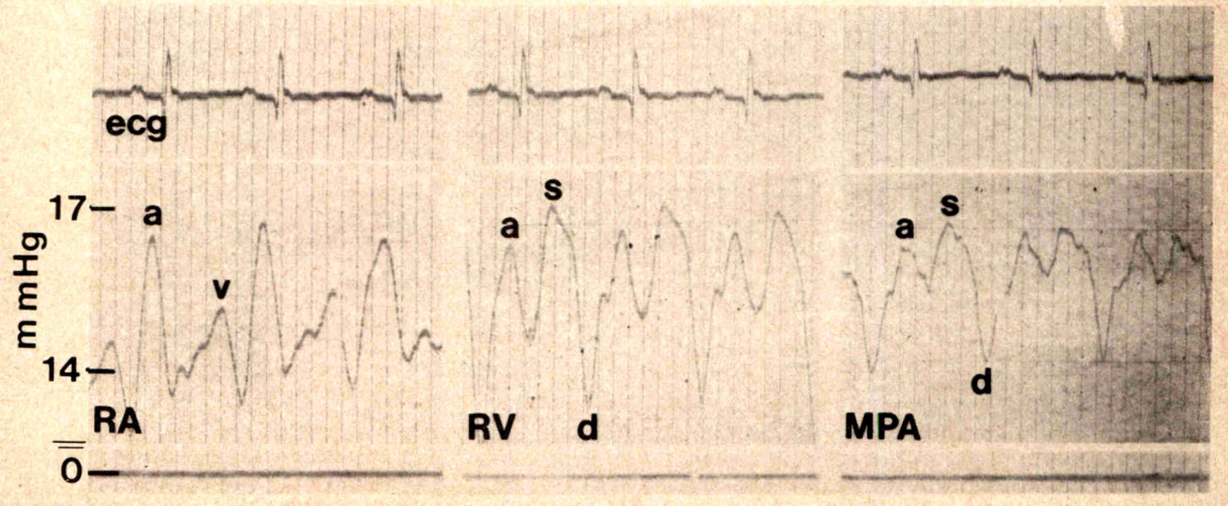

FIGURE 3. Direct catheter pressure tracings from the right atrium (RA), right ventricle (RV) and main pulmonary artery (MPA). Note prominent presystolic *a* wave (a) in the right ventricular and main pulmonary arterial tracings. d = initial diastolic; ecg = electrocardiogram; s = peak systolic; v = *v* wave.

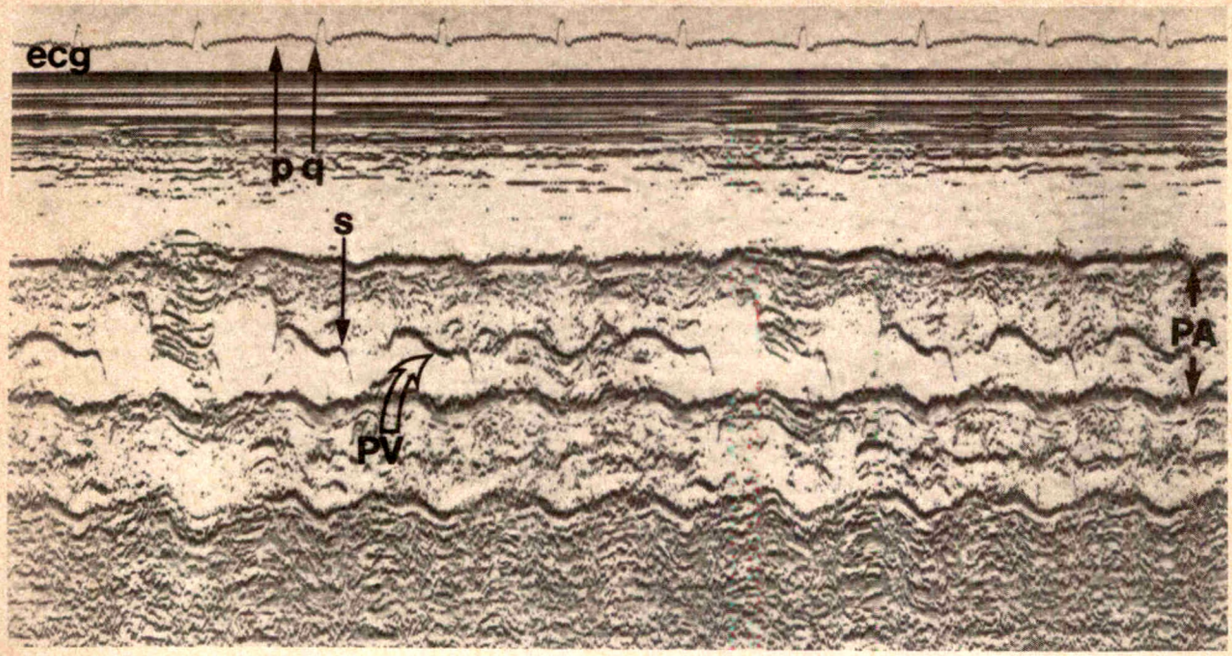

FIGURE 4. Normal pulmonary valve echogram. At the onset of systole the pulmonary leaflets separate. During the diastolic phase a single echo is seen representing the pulmonary valve. Note the minimal posterior movement of the valve just before ventricular systole. ecg = electrocardiogram; p = P wave; PV = pulmonary valve; q = Q wave; s = systole.

evidence of a normally placed tricuspid valve, a large right ventricle and absence of right ventricular trabeculae.[4,6] The pathologic finding of myocardial hypoplasia also favors a diagnosis of Uhl's anomaly.[6] Comparison of the echocardiograms described here and those reported for Ebstein's disease suggests that ultrasonic evaluation may help to differentiate Uhl's anomaly from many cases of Ebstein's disease. The tricuspid echogram in Ebstein's disease has been reported to have a decreased E-F slope, an increased excursion, a delayed closing (C point) in the absence of right bundle branch block, and an area over which the valve may be recorded that is said to be more leftward in position than in the normal tricuspid valve echogram.[25–28] Patients with Ebstein's disease are also reported to have paradoxical ventricular septal motion.[25,27] None of these criteria, except for the delayed closing of the tricuspid valve (C point), were found in our case, thus suggesting, before cardiac catheterization, that this was not classic Ebstein's disease.

Normally, the tricuspid valve closure point is not delayed more than 0.03 second and occasionally it even precedes the mitral closure.[29] Our patient did have electrocardiographic evidence of right bundle branch block, so that a delay of 0.04 to 0.05 second in closure of the tricuspid valve when compared with the mitral valve would be expected.[26] A tricuspid valve closure delay prolonged to 0.07 second falls within the range (0.04 to 1.0) reported for Ebstein's disease.[25,27] In the latter disease, the delay is thought to relate to the deformed tricuspid valve or to abnormalities of myocardial compliance or contractility. The delay in closure in our patient suggests that it may be a general sign of right ventricular myocardial dysfunction.

Other diagnostic implications: Diastolic opening of the pulmonary valve may also be a significant echocardiographic sign of right ventricular abnormality, specifically reduced compliance of either hypertrophic or hypoplastic origin, and the finding should virtually exclude pulmonary hypertension as a diagnostic possibility. In the absence of clinical evidence of pulmonary stenosis, abnormalities of the right ventricle and tricuspid valves such as Ebstein's disease or right ventricular cardiomyopathy are particularly suspect.

The significance of the pattern of mitral valve prolapse is not clear, although it has been reported in other forms of cardiomyopathy and may be an additional indication of more extensive myocardial disease.[30]

Acknowledgment

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Echocardiogram in Calcified Mitral Anulus

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Calcification of the anulus fibrosus of the mitral valve presents a characteristic pattern on the echocardiogram. This pattern may be mistaken for that of a posteriorly situated pericardial effusion. Two illustrative cases are presented.

Calcification of the anulus fibrosus of the mitral valve is a frequent finding in the elderly. Radiographically, it appears as a C- or J-shaped density overlying or just to the left of the spine in the posteroanterior view (Fig. 1). It is often an unexpected finding, although a systolic murmur is almost always present. We describe herein the echocardiographic appearance of calcification in the mitral ring and stress the potential for confusion with the pattern of pericardial effusion. The transducer was positioned in the fourth left intercostal space, with the patient in the supine position. Echocardiograms were taken with a 100 series Unirad interfaced with a model DR 8 Electronics for Medicine recorder, and a 2.25 megahertz focused transducer.

Case Reports

Case 1: A 90 year old woman had had congestive heart failure for 8 months. Physical examination revealed a fourth heart sound, a grade 3/6 holosystolic ejection murmur that was heard at both the apex and base. The electrocardiogram showed a left bundle branch block pattern with a P-R interval of 0.20 second. The chest roentgenogram (Fig. 1) disclosed a J-shaped density 1 cm in thickness just to the left of the spine, representing calcification of the mitral anulus.

In the echocardiogram, a dense band of echoes was evident that moved parallel to the posterior left ventricular endocardium and obliterated the echo from the posterior mitral leaflet (Fig. 2A). With decrease in the gain (arrow), the echoes from the calcified anulus could be mistaken for those of the posterior left ventricular wall. The echo-free space posterior to the calcified ring and anterior to the persisting epicardial echo could be erroneously interpreted as a pericardial effusion. When a sweep was made from the aorta toward the left ventricle (Fig. 2B), the echoes from the calcified ring appeared abruptly.

Case 2: A 77 year old woman had a 10 year history of atrial fibrillation and orthopnea. A grade 3/6 holosystolic murmur was heard best at the apex, radiating well to the axilla and to the base. Calcification in the mitral anulus was not apparent in the chest roentgenogram but was seen on cinefluoroscopic examination.

The echocardiogram showed a band of echoes moving parallel to the endocardium of the posterior left ventricular wall. The anular calcification could be mistaken for the endocardium, the endocardium for the epicardium, and the left ventricular wall for a pericardial effusion (Fig. 3A). A sweep from the left ventricle to the left atrium (Fig. 3B) revealed, as in Case 1, the abrupt termination of anular echoes.

Discussion

Calcification of the anulus fibrosus is a common finding at autopsy in the elderly,[1–3] and may be recognized antemortem by the characteristic appearance of the calcific deposits on roent-

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genographic or fluoroscopic examination. It is rarely found in people younger than 70 years of age, although ring calcification has been described in a young patient with Marfan's syndrome.[4] It is usually associated with a systolic murmur that may sound like the murmur of aortic stenosis, mitral regurgitation or a combination of the two. Calcification of the mitral ring may be asymptomatic or may be associated with atrioventricular and intraventricular conduction disturbances, significant mitral regurgitation[5] or endocarditis.[6,7] Calcific deposits may extend to the leaflets of the aortic valve, and associated calcific aortic stenosis may be present.

In the echocardiogram, calcification in the mitral ring appears as dense echoes that move parallel to the endocardium of the posterior left ventricular wall and may overlie or obliterate echoes coming from the posterior mitral leaflet. The dense band of echoes may extend as far down as the papillary muscles and can usually be followed up into the left atrium where it terminates abruptly. The echocardiogram may show mitral ring calcification when it does not appear on the plain chest X-ray film and can only be demonstrated radiographically by fluoroscopy. The echocardiographic appearance may mimic a pericardial effusion in which the calcified ring is mistaken for the endocardium, the endocardium for the epicardium and the epicardium for the pericardium. The diagnosis of calcified mitral anulus may be differentiated from that of pericardial effusion by demonstrating the abrupt termination of mitral ring echoes during a sweep from the left ventricle to the left atrium. In contrast, there is a gradual diminution of the posterior or echo-free space in true pericardial effusion (Fig. 4).

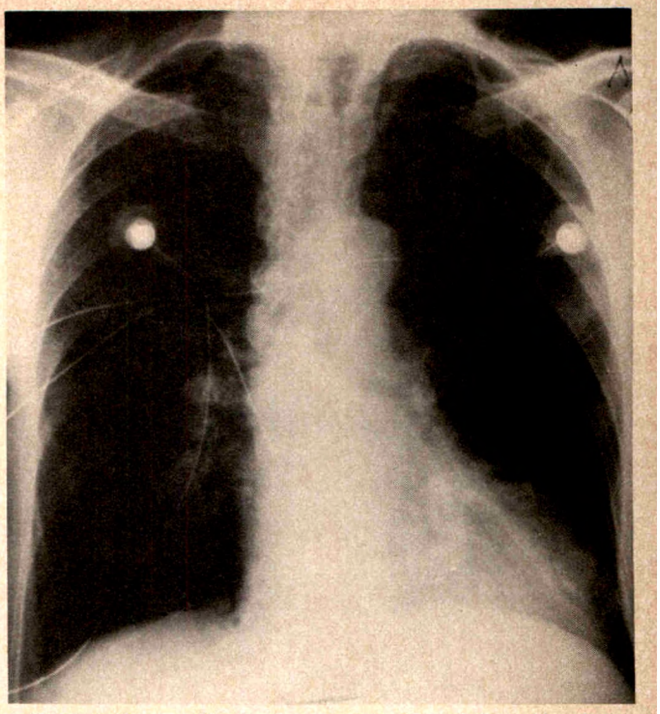

FIGURE 1. Case 1. Chest roentgenogram. Note J-shaped band representing calcific deposits in the mitral anulus.

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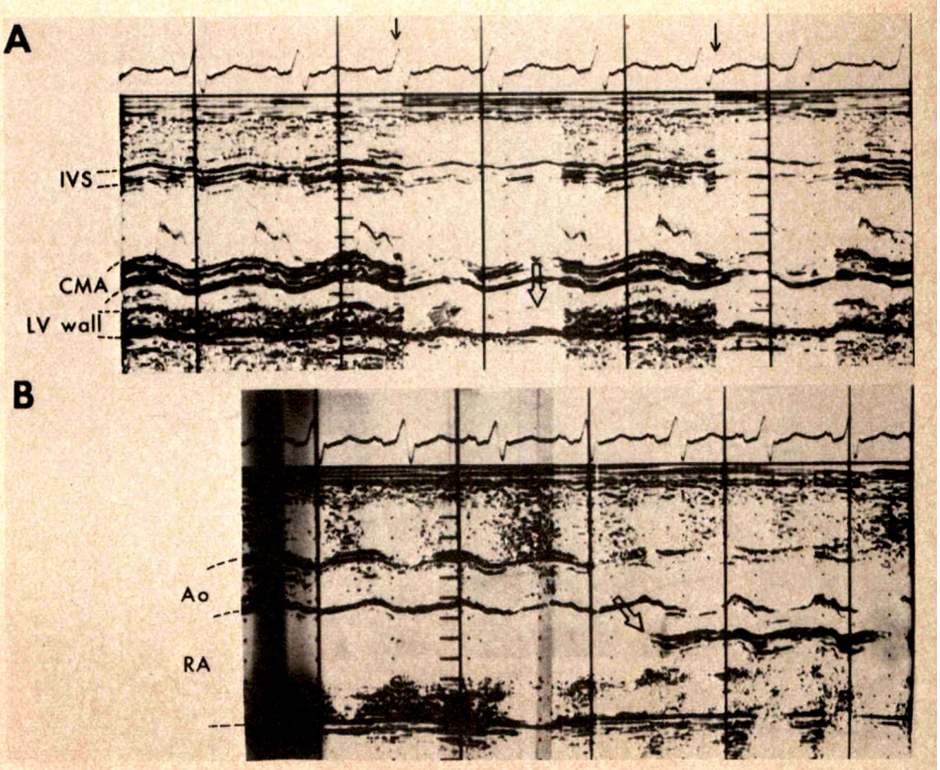

FIGURE 2. Case 1. **A,** dense echoes from the calcified mitral anulus move parallel to the posterior left ventricular endocardium. When the gain is decreased **(upper arrows),** the pattern of a posteriorly situated pericardial effusion is mimicked. On close inspection, a faint endocardial echo is visible **(lower arrow). B,** sweep from aorta toward the left ventricle shows abrupt appearance of echoes from calcified mitral anulus **(arrow).** Ao = aorta; CMA = calcified mitral anulus; IVS = interventricular septum; LV = left ventricle; RA = right atrium.

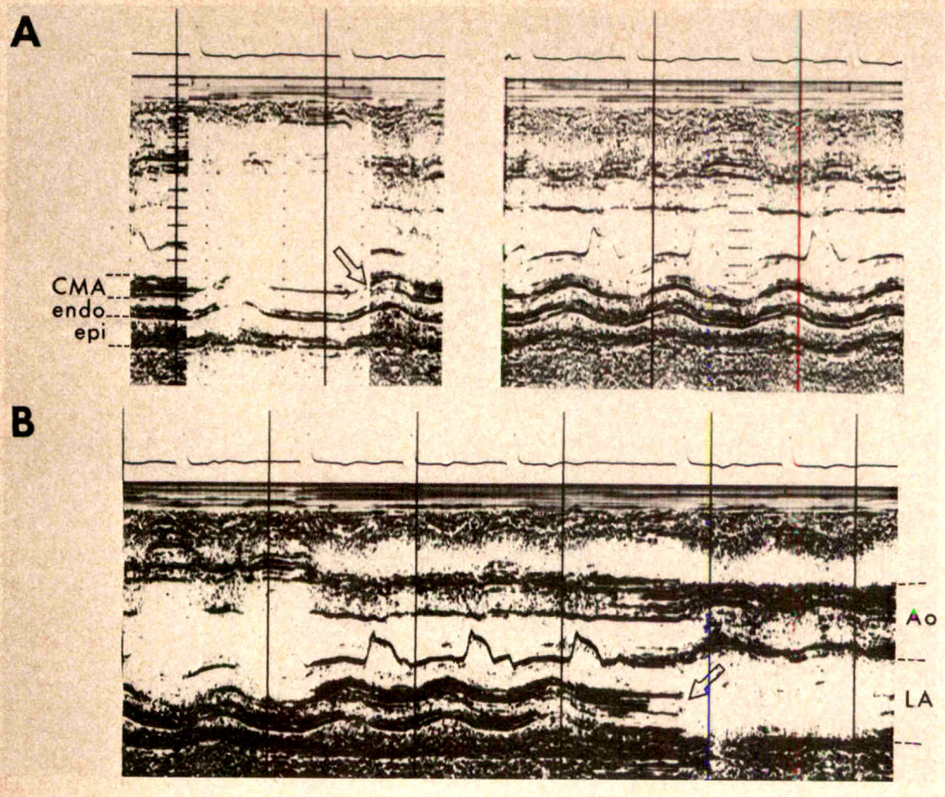

FIGURE 3. Case 2. **A,** anular echoes **(arrow)** mimic those from the endocardium. The space between the endocardium and epicardium can be mistaken for pericardial effusion. **B,** a sweep from the left ventricle to the left atrium shows abrupt termination of anular echoes **(arrow).** endo = endocardium; epi = epicardium; LA = left atrium; other abbreviations as in Figure 2.

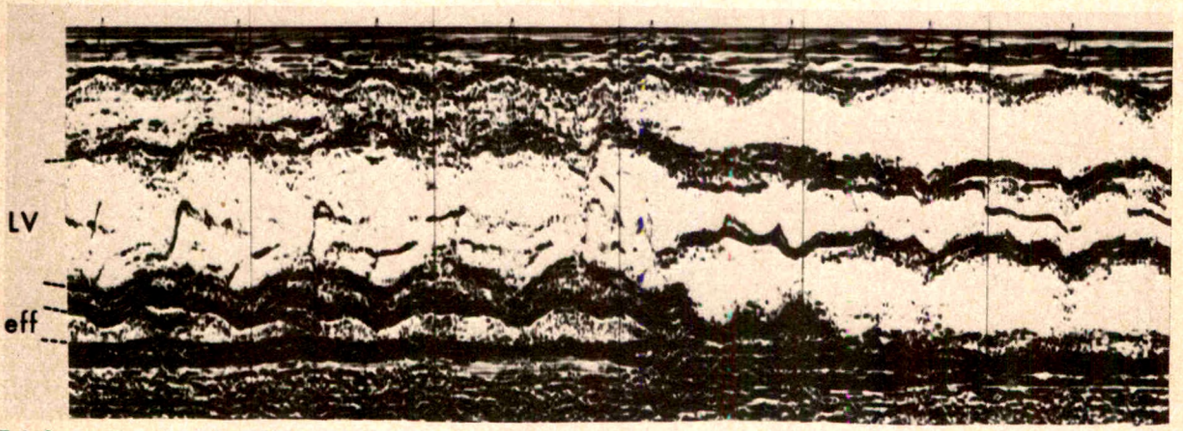

FIGURE 4. Sweep from the left ventricle to the left atrium in a patient with documented pericardial effusion. Note the gradual obliteration of the echo-free space. Note also the effusion situated anteriorly. eff = effusion; other abbreviations as in Figure 2.

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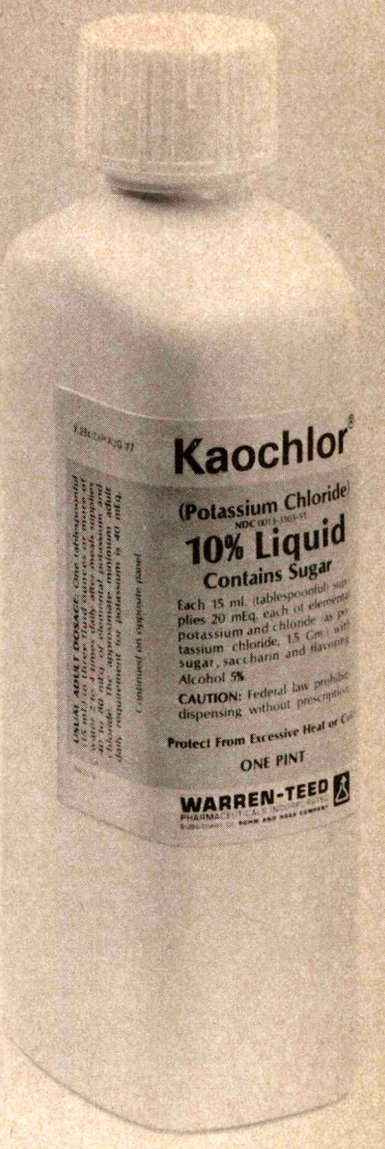

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In Cardiovascular Clinics (Albert N. Brest, MD, Editor-in-Chief) the current issue is

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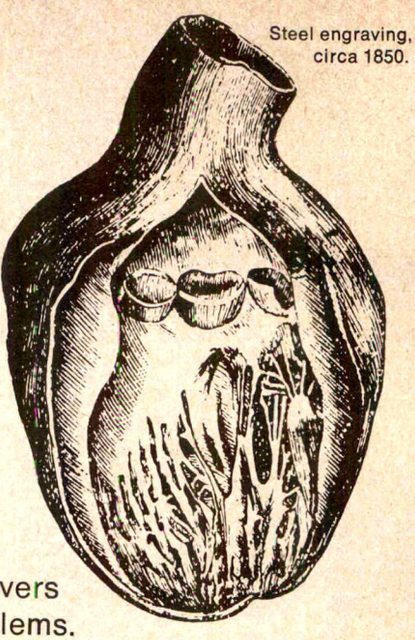

Steel engraving, circa 1850.

Edited by **Donald G. Vidt, MD**

This issue of the Cardiovascular Clinics comes from the well-known and highly regarded Cleveland Clinic and covers a number of commonly-encountered cardiovascular problems.

contents and contributors:

Atherosclerotic Coronary Disease in Young Men, by Juan S. Lim, MD; **Coronary Artery Disease in Young Women,** by C. Charles Welch, MD; **Prognostic Factors in Atherosclerotic Coronary Disease,** by William L. Proudfit, MD; **Unusual Forms of Coronary Artery Disease,** by Mehdi Razavi, MD; **Modern Medical Management of Angina Pectoris,** by James R. Hodgman, MD; **Selection of the Candidate for Myocardial Revascularization,** by Floyd D. Loop, MD, and Frederick A. Heupler, MD; **Surgical Treatment of Acute Coronary Insufficiency (Impending Myocardial Infarction)** by Chalit Cheanvechai, MD, and Donald B. Effler, MD; **Myocardial Revascularization in Patients Aged 65 and Older,** by Jorge M. Garcia, MD, Chalit Cheanvechai, MD, and Donald B. Effler, MD; **Results of Graft Surgery for Coronary Artery Disease: A Progress Report,** by William C. Sheldon, MD, Gustavo Rincon, MD, and Augusto Pichard, MD; **The Relationship of Hypertension to Coronary, Aortic, and Iliofemoral Atherosclerosis,** by Harriet P. Dustan, MD; **The Heart in Hypertension,** by M. Mohsen Ibrahim, MD, and Robert C. Tarazi, MD; **The Hypertensive Evaluation: To What Extent is it Necessary?** by Donald G. Vidt, MD; **Practical Clinical Pharmacology of Antihypertensive Drugs,** by Ray W. Gifford, Jr., MD; **The Evaluation of Common Heart Murmurs in the Adult by Noninvasive Techniques,** by Wayne Siegel, MD; **Angina Pectoris and Aortic Valve Disease,** by Royston C. Lewis, MD, and Antonio B. Creus, MD; **Beta-Adrenergic Blockade in Some Cardiovascular Diseases,** by Robert C. Tarazi, MD; **The Role of Myocardial Biopsy in Cardiac Diagnosis,** by Earl K. Shirey, MD, and William A. Hawk, MD; **Understanding the Cardiac Pacemaker: Followup Evaluation,** by Lon Castle, MD; **The Ischemic Leg: A Clue to Dissecting Aneurysm,** by Jess R. Young, MD, John Kramer, MD, and Alfred W. Humphries, MD.

222 pages, 65 illustrations. $23

next issue due October 1975

INNOVATIONS IN THE DIAGNOSIS AND MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

By Albert N. Brest, MD; Leslie Wiener, MD; Edward K. Chung, MD; and Hratch Kasparian, MD.

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Each tablet contains: Catapres®, brand of clonidine hydrochloride, 0.1 or 0.2 mg and chlorthalidone, 15 mg

The only major new combination antihypertensive in a decade

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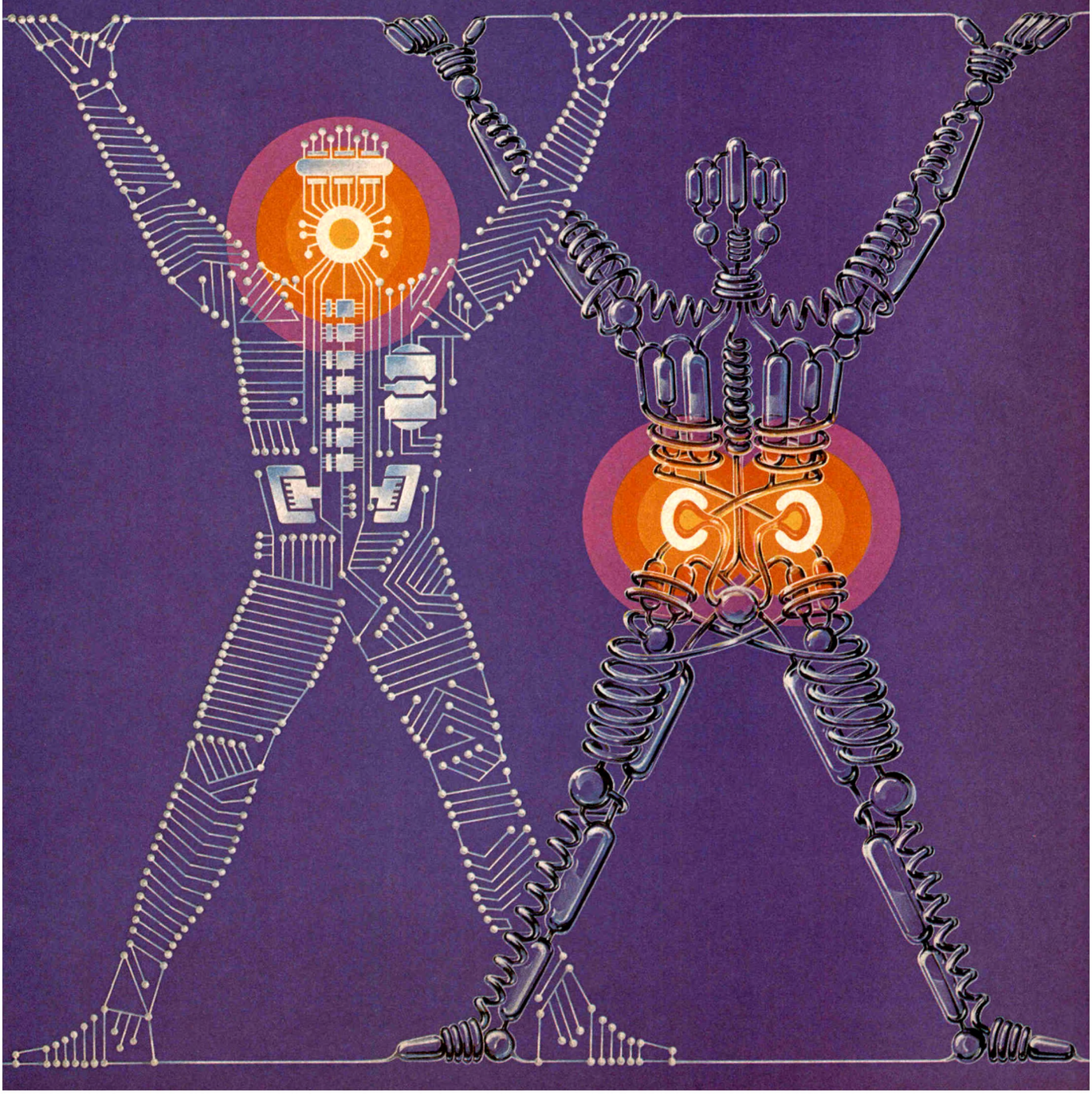

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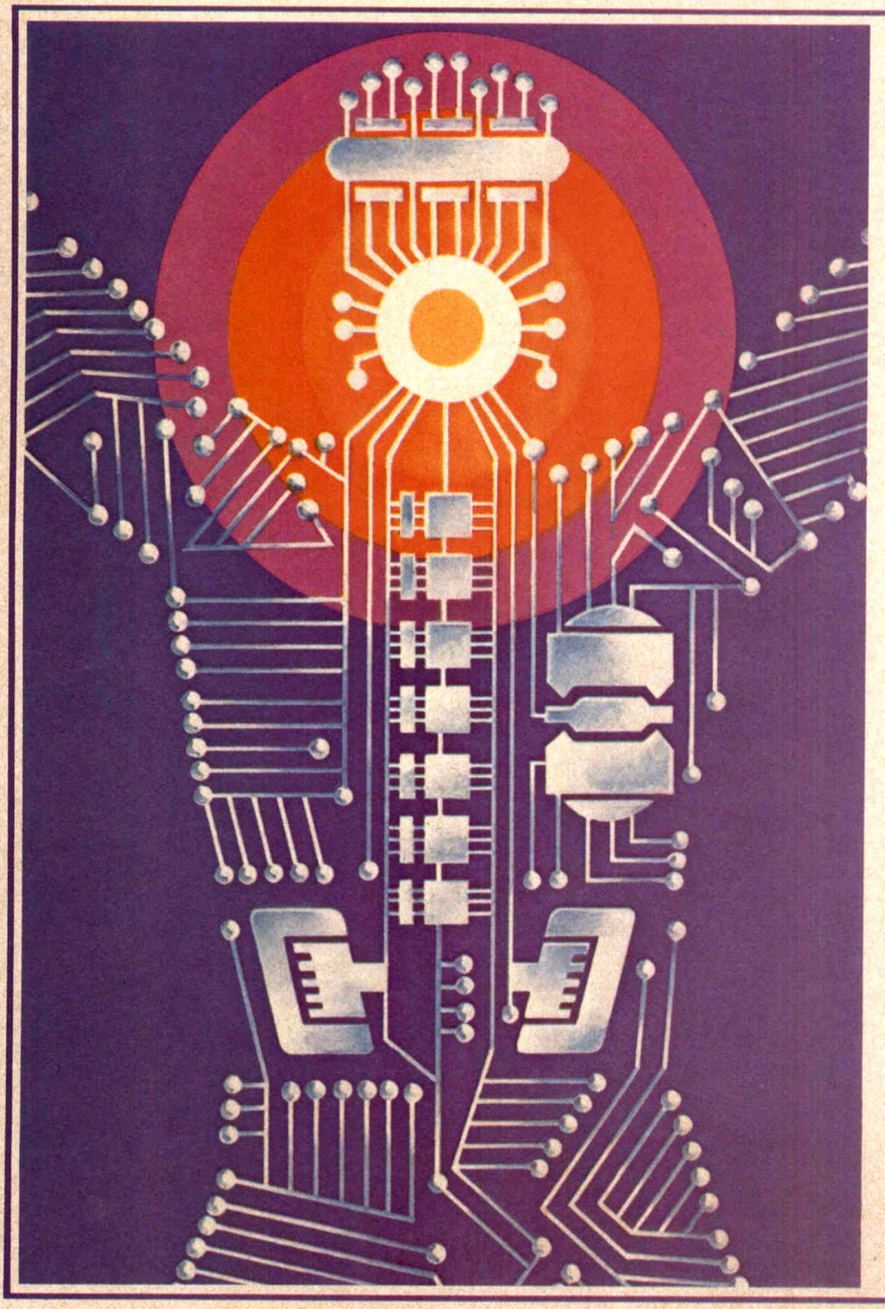


Catapres®
(clonidine hydrochloride)
contributes:

Action at the vasomotor centers as shown in animal studies—not a rauwolfia derivative or a sympathetic blocker or a "false transmitter"

Maximal blood pressure lowering without the weeks of delay common with the rauwolfia class of antihypertensives

Significant blood pressure reduction without alteration of normal hemodynamic responses to exercise

Mild and infrequent orthostatic hypotension

Little or no change in renal blood flow and glomerular filtration rate

Reduced plasma renin activity and excretion of aldosterone and catecholamines (see Actions section)

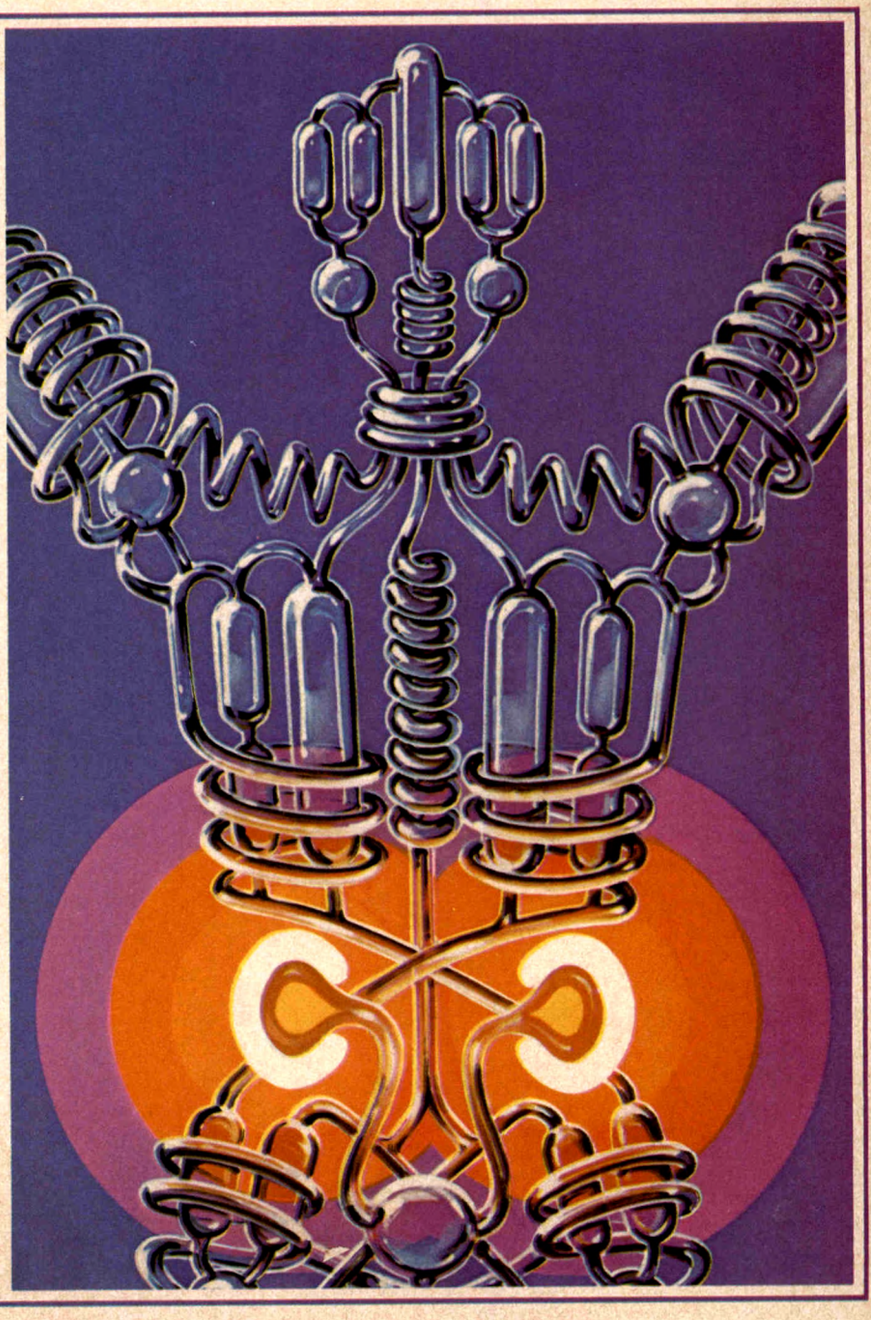
Combines Catapres (clonidine hydrochloride) with a diuretic—the only major new combination antihypertensive in a decade

Chlorthalidone contributes:

Pharmacologic action similar to the thiazides

Smooth, extended diuretic/antihypertensive effect

Additive or potentiating effect on adjunctive antihypertensive agents



The most common adverse reactions with Combipres are dry mouth, drowsiness, and sedation. As with thiazide-containing combination antihypertensives, hypokalemia, hyperuricemia, and decreased glucose tolerance may occur. Combipres is contraindicated in patients with known sensitivity to chlorthalidone and in those with severe renal or hepatic disease.

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See box Warning on next page concerning the appropriate use of Combipres.

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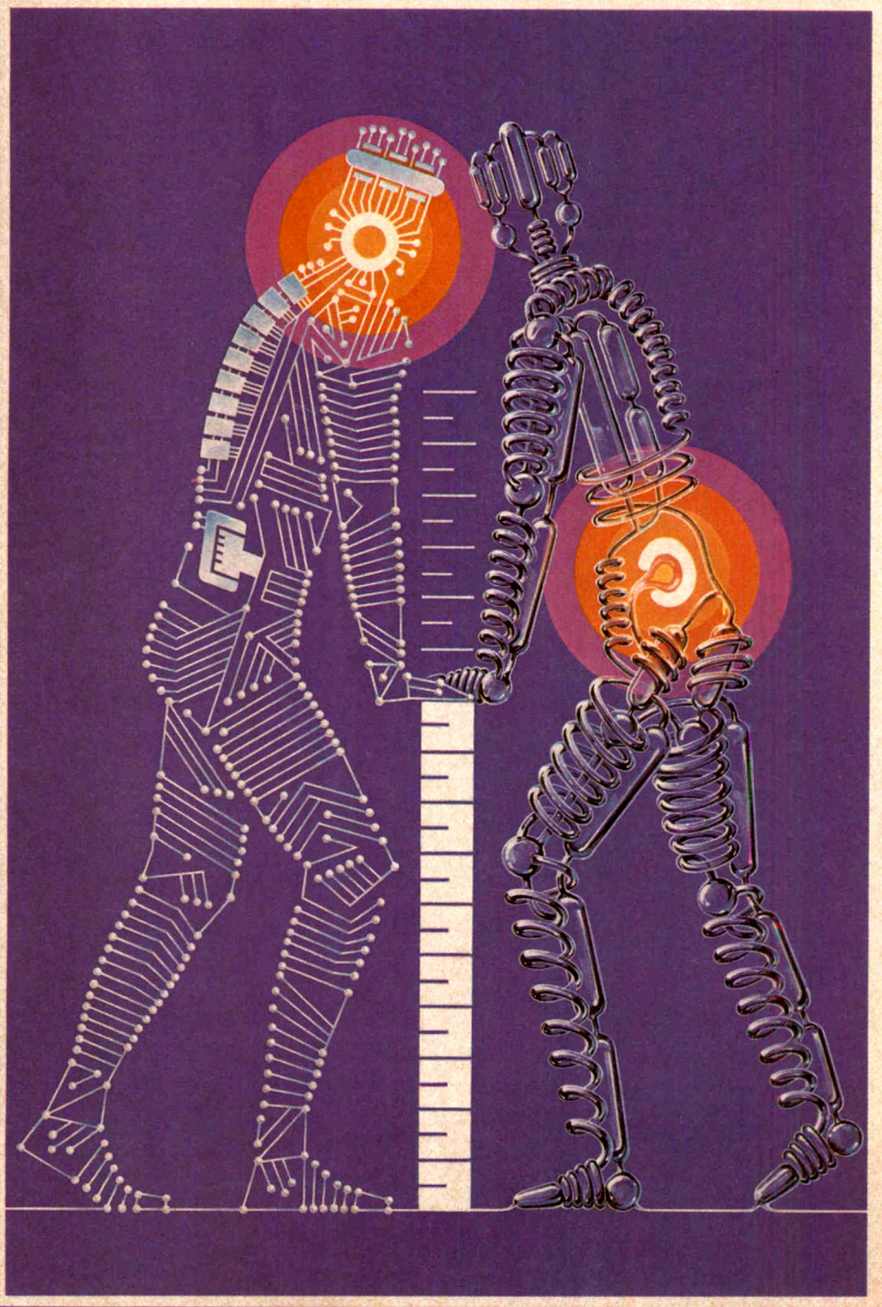


Works harder

Usually exerts a more pronounced antihypertensive effect than either component alone in equivalent doses*

Works broadly

Wide therapeutic range—mild to severe hypertension

Works conveniently

Simplifies therapy for the hypertensive patient who needs more than one drug*

Works for less

Costs less than two separate prescriptions*

Works and work and works

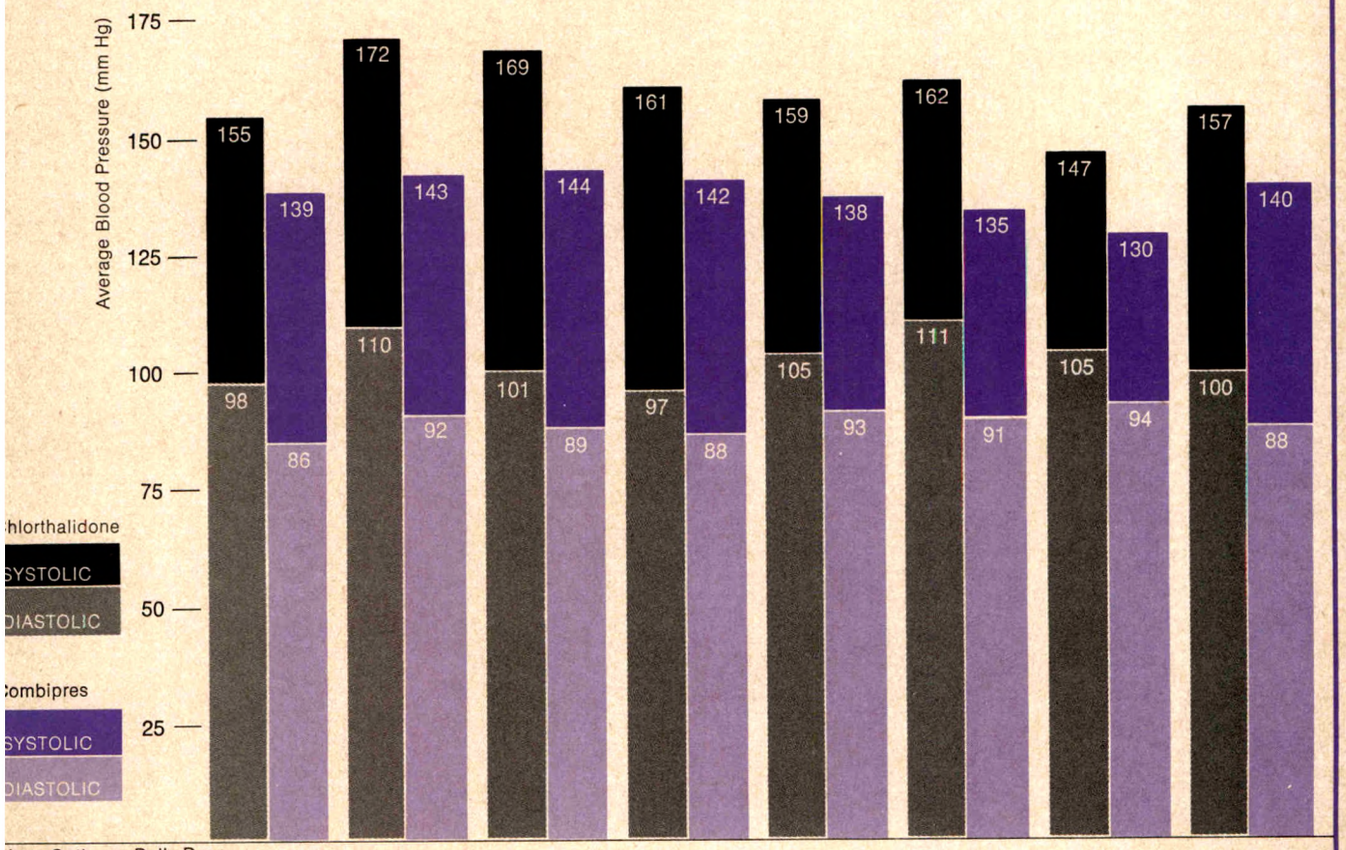
Convenience and economy encourage patients to stay on medication, help assure continued blood pressure control over the long course of therapy*

*__WARNING__ Combipres is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

The only major new combination antihypertensive in a decade

Works in the majority of hypertensive patients

Chlorthalidone vs Combipres
A Comparison of Standing Blood Pressure Response in 8 Studies



Mean Optimum Daily Dose Chlorthalidone (mg)	50	50	47.7	50	50	50	71	50
Combipres (mg)	0.3	0.48	0.47	0.4	0.43	0.68	0.52	0.4
No. of Patients who completed study	42	20	11	17	34	9	31	9
Study	1	2	3	4	5	6	7	8

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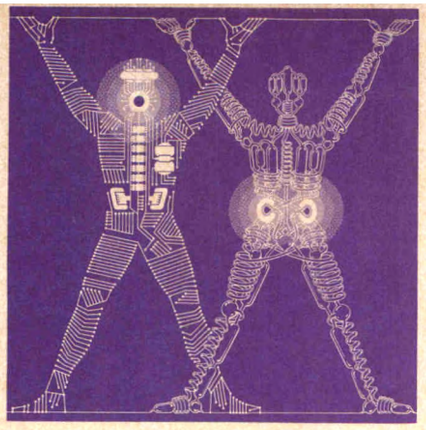

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Each tablet contains: Catapres®, brand of clonidine hydrochloride, 0.1 or 0.2 mg and chlorthalidone, 15 mg

Guidelines for Titrating Catapres and Chlorthalidone Dosages:

Initial doses: Catapres—one 0.1 mg tablet twice daily. Chlorthalidone—50 mg daily.

Dosage increments: While daily chlorthalidone doses remain at 50 mg, further increments of Catapres of 0.1 mg or 0.2 mg per day can be made at intervals of 2 to 14 days depending on severity of hypertension. The usual daily dose of Catapres ranges between 0.2 and 0.8 mg. Studies indicate that 2.4 mg is the maximum effective daily dose, but doses as high as this have rarely been used.

Combipres®

Each tablet contains:
Catapres®, brand of clonidine hydrochloride, 0.1 or 0.2 mg and chlorthalidone, 15 mg

WARNING: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Actions: Catapres (clonidine hydrochloride): The mechanism of action appears to be central alpha-adrenergic stimulation as demonstrated in animal studies. This results in inhibition of bulbar sympathetic cardioaccelerator and sympathetic outflow from the brain. Other studies in humans have provided evidence of a reduction in plasma renin activity and the excretion of aldosterone and catecholamines. The exact relationship between these pharmacologic actions of Catapres (clonidine hydrochloride) in humans and its antihypertensive effect has not been fully elucidated at this time.

Chlorthalidone: The diuretic action of chlorthalidone is thought to be due to inhibition of sodium and chloride reabsorption in the proximal tubule.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastri irritation, anorexia, constipation and cramping, we ness, dizziness, transient myopia and restlessnes are occasionally observed. Headache and impoter or dysuria may occur rarely. Orthostatic hypotensi has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbitura or narcotics. Skin rashes, urticaria and purpura h been reported in a few instances.

A decreased glucose tolerance evidenced by hype glycemia and glycosuria may develop inconsisten This condition, usually reversible on discontinuati of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed shoul be checked regularly.

As with other diuretic agents hypokalemia may oc (see Precautions). Hyperuricemia may be observe on occasion and acute attacks of gout have been cipitated. In cases where prolonged and significa elevation of blood uric acid concentration is cons ered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuric mia without loss of diuretic and/or antihypertensi activity.

Idiosyncratic drug reactions such as aplastic aner thrombocytopenia, leukopenia, agranulocytosis, a necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be c sidered when epigastric pain or unexplained gast intestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reporte with this general class of compounds include: jau dice, xanthopsia, paresthesia and photosensitizat

Overdosage: ***Catapres (clonidine hydrochloride)*** Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting follow the accidental ingestion of Catapres by several ch dren from 19 months to 5 years of age. Gastric lav and administration of an analeptic and vasopress led to complete recovery within 24 hours. Tolazoli in intravenous doses of 10 mg at 30-minute interv abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances o electrolyte balance. There is no specific antidote, gastric lavage is recommended, followed by supp tive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet cont clonidine hydrochloride, 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-score compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride, 0.2 mg + chlorthalidone, 15 mg). available as blue, oval, single-scored compresse tablets in bottles of 100.

For complete details, please see full prescribing information.

References: 1. Becker, M. C.: Data on file at Boehringer Ingelheim Ltd. **2.** Belle, M. S.: Data on at Boehringer Ingelheim Ltd. **3.** Hall, B. H.: Data file at Boehringer Ingelheim Ltd. **4.** McDonald, R. Data on file at Boehringer Ingelheim Ltd. **5.** Parso W. B., Jr.: Data on file at Boehringer Ingelheim L **6.** Russell, R. P.: Data on file at Boehringer Ingelhe Ltd. **7.** Winemiller, R. H.: Data on file at Boehring Ingelheim Ltd. **8.** Yeh, B.: Data on file at Boehrin Ingelheim Ltd.

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Sounds of the human body occur in the most widely varying frequency ranges. A doctor should have three stethoscopes to properly measure all sounds. You can now have three stethoscopes in one with the new Bosch EST 40 Electronic Stethoscope.

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Order your Electronic Stethoscope today! Send the coupon on the right with your $275 payment (the complete purchase price). Try the instrument in your office for 30 days. Satisfaction assured or your money will be refunded when you return the instrument at the end of your trial period.

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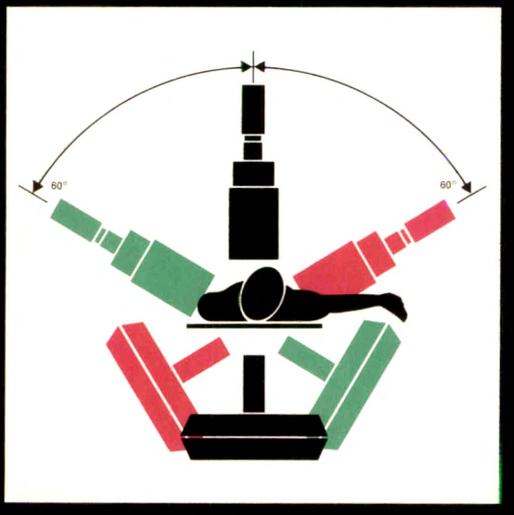
Four why's to improv
one way...with Philip

1

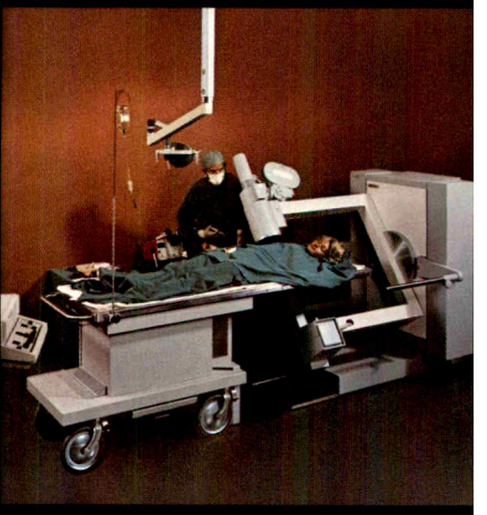
The patient remains stationary during catheterization.



Why? Because the Cardio Diagnost's U-arm rotates the X-ray beam around the patient. And the entire U-arm can be raised or lowered effortlessly. An easier, more efficient examination... a stationary, comfortable, more cooperative patient.

2

You can scan freely in any patient plane... with one hand.



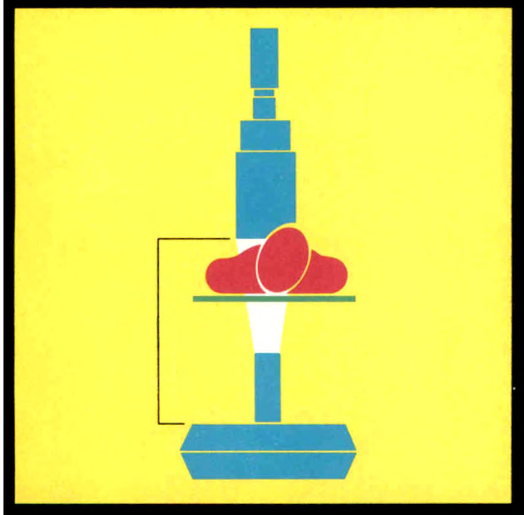
Why? Superb engineering. With one hand and virtually no effort, you can elevate, lower or rotate the U-arm to scan freely in any patient plane. The scanning motion can be locked at right angles to the central ray and scanning can be kept close to the chest wall. Your other hand is free for catheter control.

PHILIPS®

ardiac angiography
ardio Diagnost

3

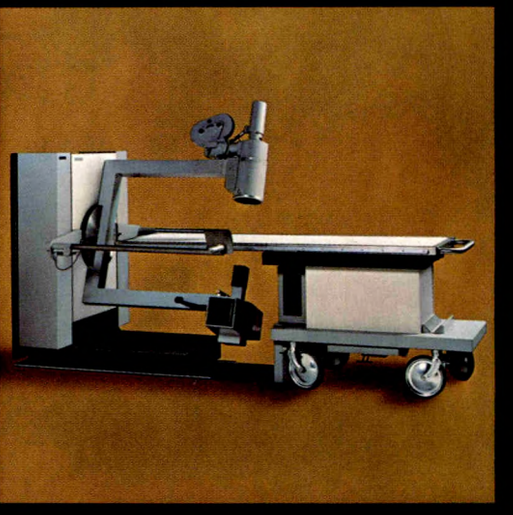
The finest image quality available... in fluoroscopy and 35mm cine.



Why? Philips 6″ Image Intensifier provides the finest contrast and resolution available. The I.I. is close to the chest wall; the distance from tube to intensifier is fixed; beam collimation is precise.

4

A built-in patient transfer system.



Why? Because the Cardio's examination table is actually a mobile cart. The patient can be prepped, examined and wheeled to a post-op room on the same table. Multiple carts make this feature extremely valuable wherever cardiac angiography is a routine procedure.

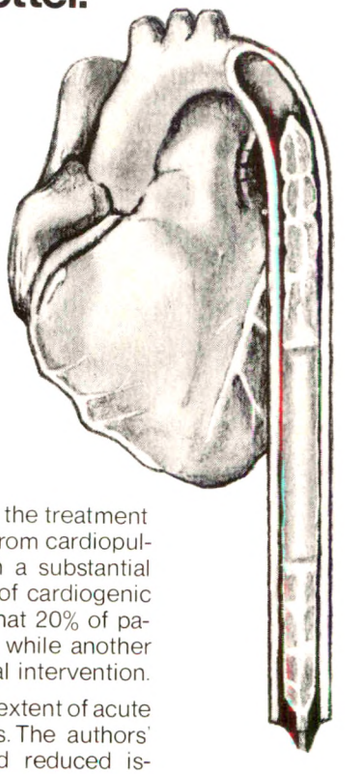
Need more why's? Ask any one of our many satisfied users. Or write us. We'll provide all you need... or show you the one way in a major institution near you.

PHILIPS MEDICAL SYSTEMS, INC

"a life-saving measure in a substantial minority of patients"[1]

The Avco Intra-Aortic Balloon Pump* ...and the Sooner, the Better.

The rationale of intra-aortic balloon pump (IABP) therapy in low-cardiac output conditions is widely accepted. By lowering pressure in the proximal aorta at the beginning of systole, myocardial work load is lessened. Also, by augmenting pressure during early diastole, pumping improves coronary perfusion and can open dormant collaterals. Thus a better balance between myocardial oxygen demand and consumption is obtained.



Documented effectiveness

The IABP's effectiveness is clinically proven in the treatment of cardiogenic shock and in weaning patients from cardiopulmonary bypass. It is a "lifesaving measure in a substantial minority of patients who would otherwise die of cardiogenic shock."[1] Braunwald and Maroko[2] estimate that 20% of patients who would otherwise die can be saved, while another 20% can be stabilized for diagnosis and surgical intervention.

IABP "significantly reduced the magnitude and extent of acute myocardial ischemic injury"[3] in animal studies. The authors' preliminary clinical results also demonstrated reduced ischemia as well as hemodynamic improvement.

Time a critical factor

Hemodynamic criteria to determine if a patient who seems to be going into cardiogenic shock is responding to treatment have been developed by Leinbach.[4] These criteria are a major contribution to the effective application of IABP treatment since *early use* of the system greatly increases the chances of success. Buckley and associates[5] used the IABP in 27 heart-surgery patients who went into shock upon termination of cardiopulmonary bypass. Eighteen survived; 13 are long term survivors. Best results occurred with initiation of IABP therapy early in the postoperative period.

*Developed by Avco Corporation and manufactured for Roche Medical Electronics Division.

The IABP versus drugs

Dunkman and others[6] have concluded that "catecholamines may actually increase ventricular dysfunction and necrosis" whereas the IABP's enhancement of coronary perfusion and reduction of oxygen-consuming work in the left ventricle can save patients if applied before about 40% of the left ventricle is irretrievably damaged. Moreover, IABP permits safe use of drugs if needed.

AVCO, the most experienced system

The internal counterpulsation system most widely used clinically is the Avco IABP. There are some very practical reasons for this dominance.

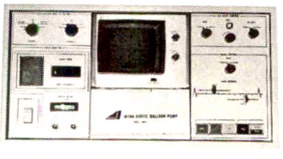
Patented 3-chamber balloon design prevents end occlusion.

QRS triggered synchronization with normal and abnormal rhythms.

Automatic reset for changes in interval or loss of R wave.

Safety engineering with fail-safe venting, self-initiated trouble identification, and emergency compressor with independent power supply.

Nationwide on-site service.



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2. Braunwald, E. and Maroko, P.R., Ann. Int. Med. 76:659, 1972.
3. Maroko, P.R. et al. Circulation 45:1150, 1972.
4. Leinbach, R.C., quoted in Emerg. Med. 5:107, 1973.
5. Buckley, M.J. et al (abstract). Circulation 46, Suppl. 2:76, 1972.
6. Dunkman, W.B. et al. Circulation 46:465, 1972.

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Write for information on clinical experience and the annual Avco Pump Users' Meeting. Your local representative can arrange an Avco IABP demonstration in either a clinical or experimental setting.

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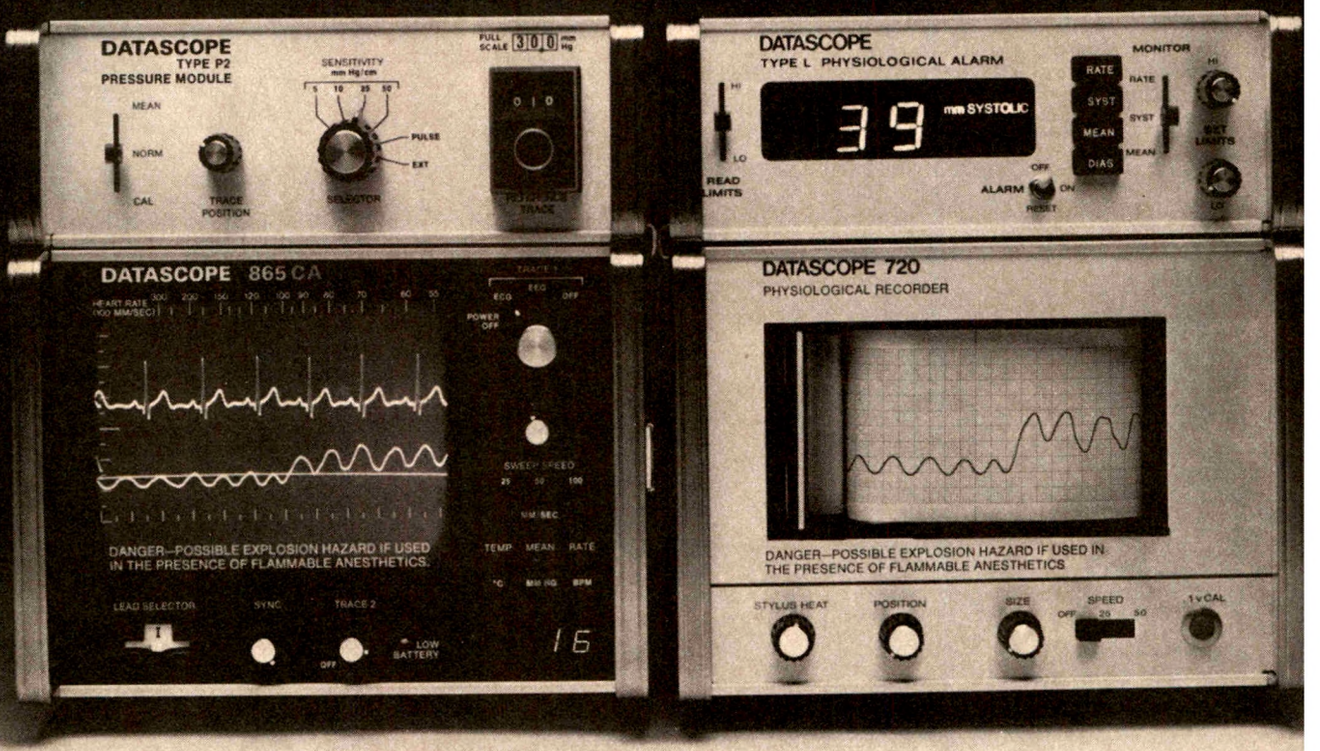

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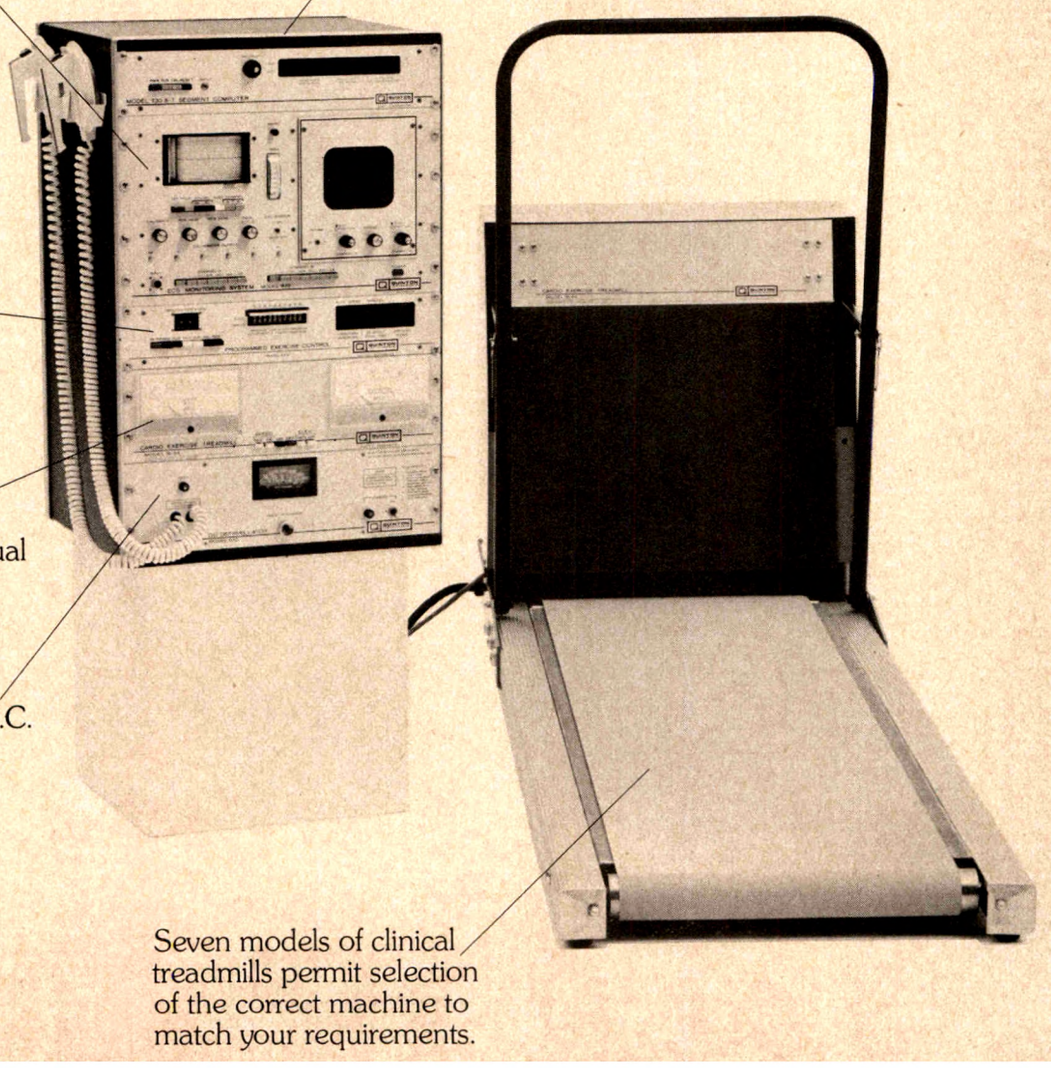

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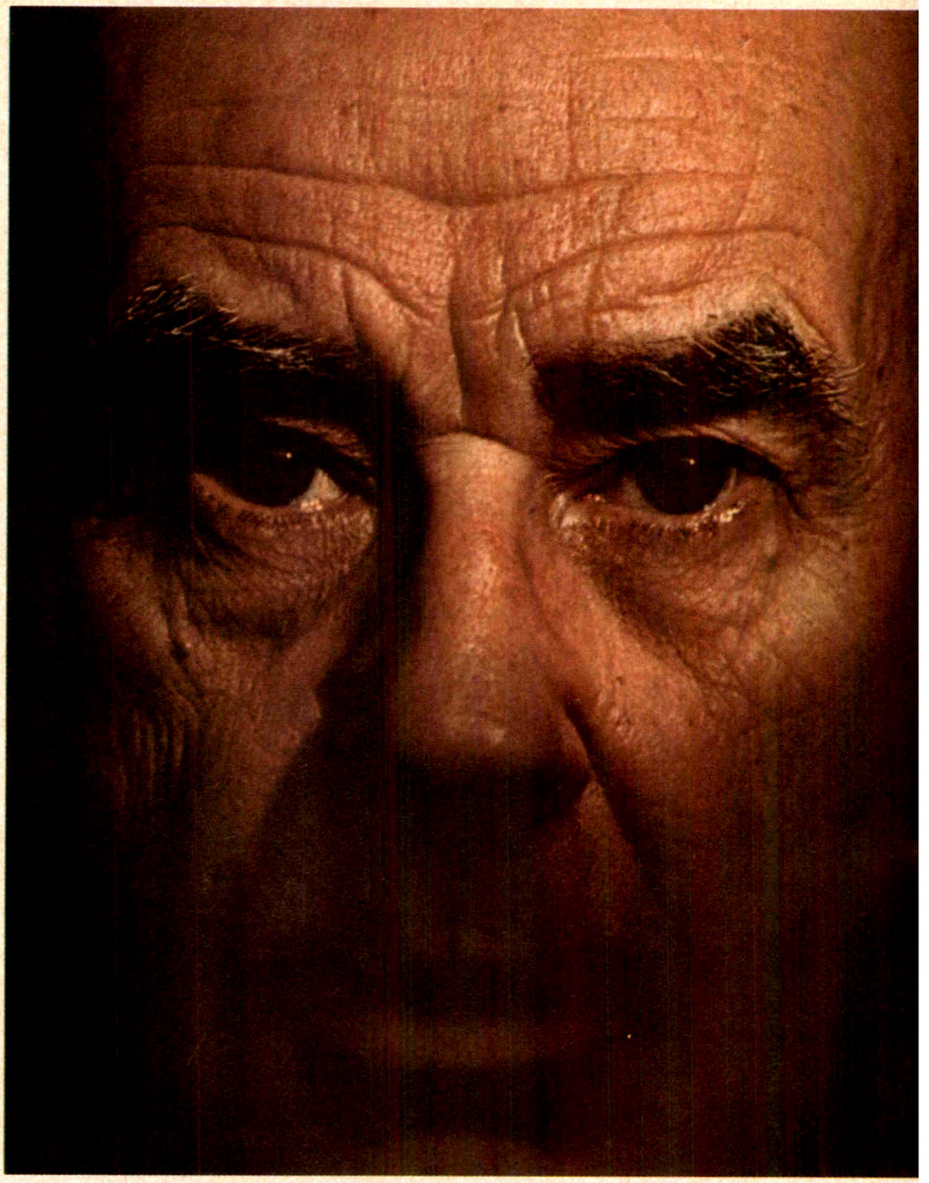
This thermographic study offers objective evidence of circulatory improvement.

Heretofore, subjective evaluations have cast doubt on the efficacy of cerebral vasodilators in increasing blood flow. Now, for the first time, thermography furnishes *objective* evidence of the case for Cerespan® (papaverine HCl): in a series of 9 patients, an "increase in cerebral blood flow due to the direct vasodilating effect of Cerespan (papaverine hydrochloride)."[1]



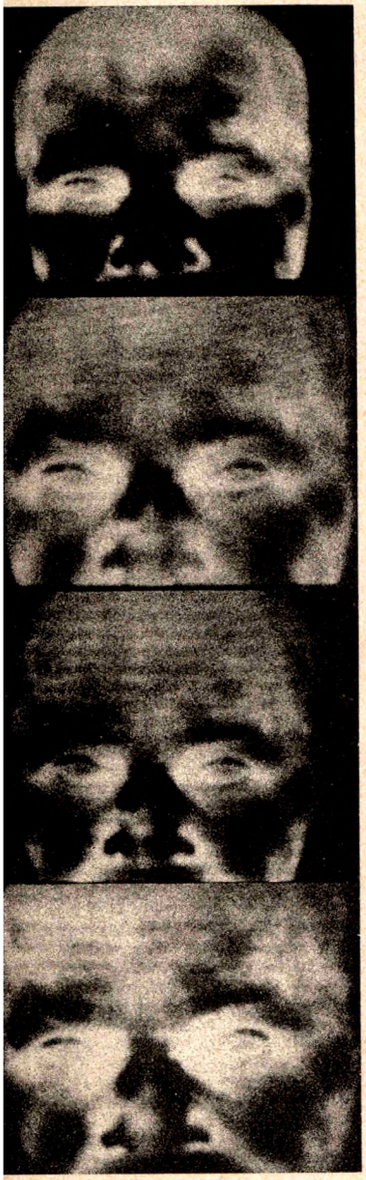
This photograph of a professional model illustrates the supraorbital and frontal areas studied thermographically in this investigation.

Rationale of the study—Thermography is a precise, simple means of measuring surface temperature. In a selected area of the body it can be used to estimate changes in blood flow by measuring the associated temperature changes.[2] It is not used for the assessment of cerebral function.

Unlike angiography, thermography is atraumatic and noninvasive.[1,2] A high degree of correlation between thermographic and angiographic studies in cerebral vessels has been observed. In evaluating the results of endarterectomy at the Neurological Institute of New York, the two techniques agreed in 95% of 119 patients.[3] "From the practical standpoint it is no longer considered essential to perform angiography if the thermogram reverts to normal."[3]

The supraorbital and frontal areas of the face were chosen for the Cerespan (papaverine HCl) study because they are perfused by branches of the ophthalmic artery, which in turn arises from the internal carotid artery. Changes in flow through the internal carotid artery, which perfuses the brain via the circle of Willis, produce corresponding changes in flow in the ophthalmic branch. These changes are detectable thermographically in the supraorbital and frontal areas.[4]

A CASE IN POINT: 8-HOUR IMPROVEMENT IN BLOOD FLOW



Control thermogram of 75-year-old male with arteriosclerotic heart disease shows severe supraorbital cooling on right, marked supraorbital and frontal cooling on left, indicating diminished blood flow to these areas supplied by branches of ophthalmic artery.

1 hour after administration of 300 mg. (2 capsules) of Cerespan, the thermogram shows very significant improvement: slight supraorbital cooling on right, slight supraorbital and frontal cooling on left.

4 hours after Cerespan was administered, improvement is maintained, no significant change is shown from 1-hour thermogram.

8 hours after Cerespan, improvement is still maintained, with no significant change from 1-hour thermogram. **Evaluation:** "very significant" improvement in blood flow to ophthalmic branch of internal carotid artery, evaluated thermographically, lasting for the entire 8-hour period of observation.

Conclusion from this study in a total of 9 patients: "These improvements in the thermograms were attributed to an increase in cerebral blood flow due to the direct vasodilating effect of Cerespan (papaverine hydrochloride)."[1]

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(papaverine HCl) q.12 h.

150 mg. in micro-dialysis cells

TO HELP INCREASE BLOOD FLOW TO THE BRAIN

in transient ischemic attacks due to vasospasm

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helps decrease vascular resistance

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For full information on the studies described here, see your USV Representative or write to: Medical Services, USV Pharmaceutical Corp., Tuckahoe, N.Y. 10707.

BRIEF SUMMARY Each Cerespan capsule contains papaverine HCl 150 mg. in micro-dialysis cells. **Indications and Dosage:** For relief of cerebral and peripheral ischemia associated with arterial spasm, 1 capsule q. 12 h. **Precautions:** Use with caution in glaucoma. Discontinue drug if hepatic hypersensitivity with gastrointestinal symptoms, jaundice, eosinophilia and altered liver function tests occur. **Adverse Reactions:** Anorexia, nausea, abdominal distress, constipation or diarrhea, skin rash, malaise, drowsiness, vertigo, sweating and headache. **Supplied:** Bottles of 100 and 1000; drums of 5000; single-dose blister packs, boxes of 500.

References: 1. Data on file, Department of Medical Research, USV Pharmaceutical Corp. 2. Karpman, H. L., Kalb, I. M. and Sheppard, J. J.: Geriatrics 27:96, 1972. 3. Wood, E. H. and Hilal, S. K.: in Extracranial Cerebrovascular Disease and its Management (Gillespie, J. A., ed.), London, Butterworths, 1969, ch. 4, p. 82. 4. Capistrant, T. D. and Gumnit, R. J.: Stroke 4:57, 1973.

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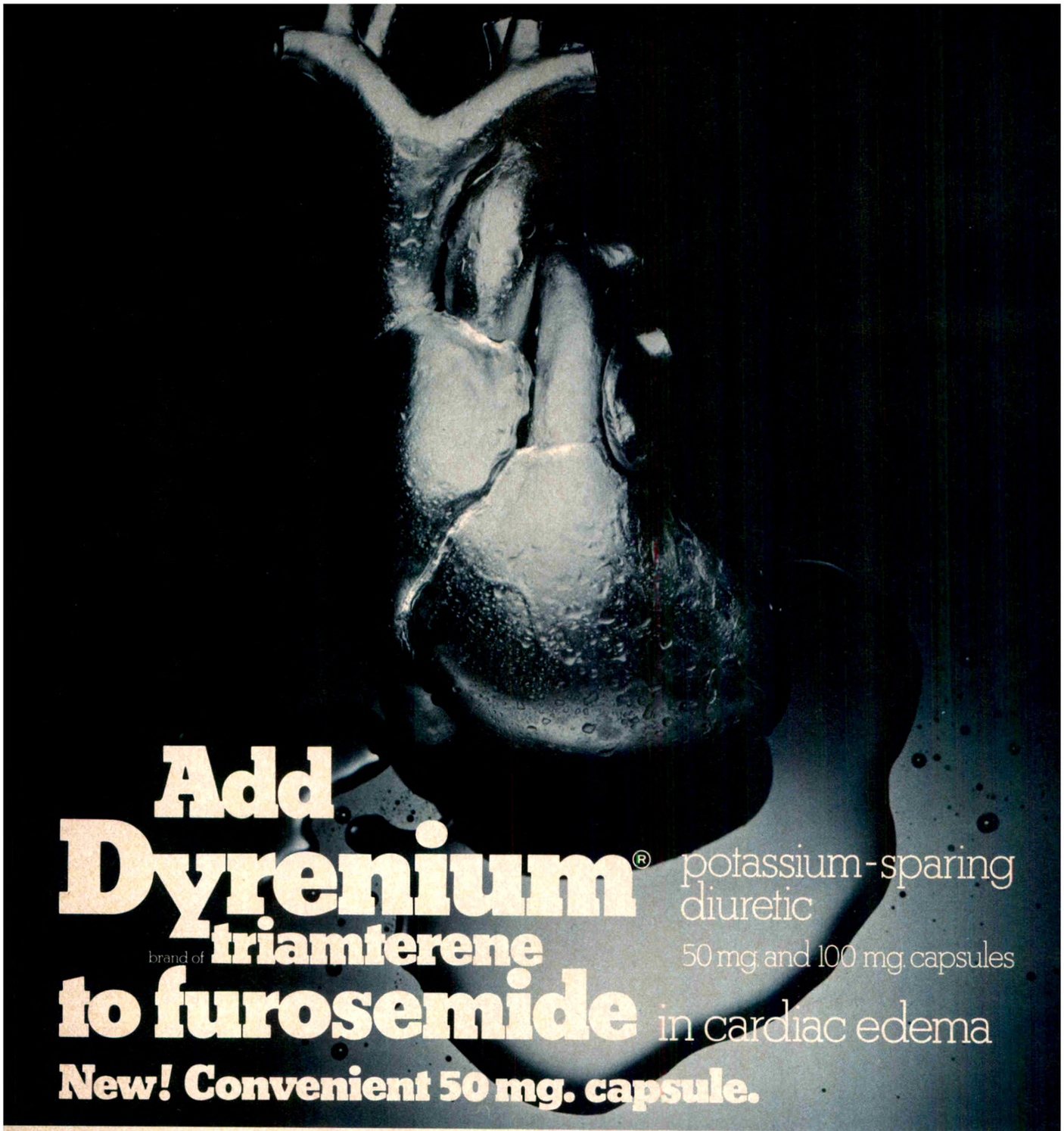

The addition of 'Dyrenium' (50 or 100 mg.) to furosemide (40 mg.) markedly increased sodium and water output in 10 normal volunteers, especially on the first day of administration. 'Dyrenium' also reduced kaliuresis in all subjects, completely blocking the kaliuretic effect of furosemide (40 mg.) in seven subjects.[1] Patients with fluid overload and abnormal physiology may respond differently from volunteers; therapy should be titrated to the individual.

1. Stote, et al.: Effect of Triamterene on Furosemide Induced Kaliuresis in Normal Volunteers, J. Int. Med. Res. 2:379-83, 1974.

Hyperkalemia can occur with any K^+-sparing agent, but it is rare if urinary output is adequate. Serum K^+ and BUN should be checked periodically; elderly, diabetics, or patients with suspected or confirmed renal insufficiency should be observed closely. When 'Dyrenium' is given with furosemide, K^+ supplements should be discontinued, and not given unless hypokalemia develops or dietary potassium intake is markedly impaired.

See facing page for indications and brief summary of prescribing information.

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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

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Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

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Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

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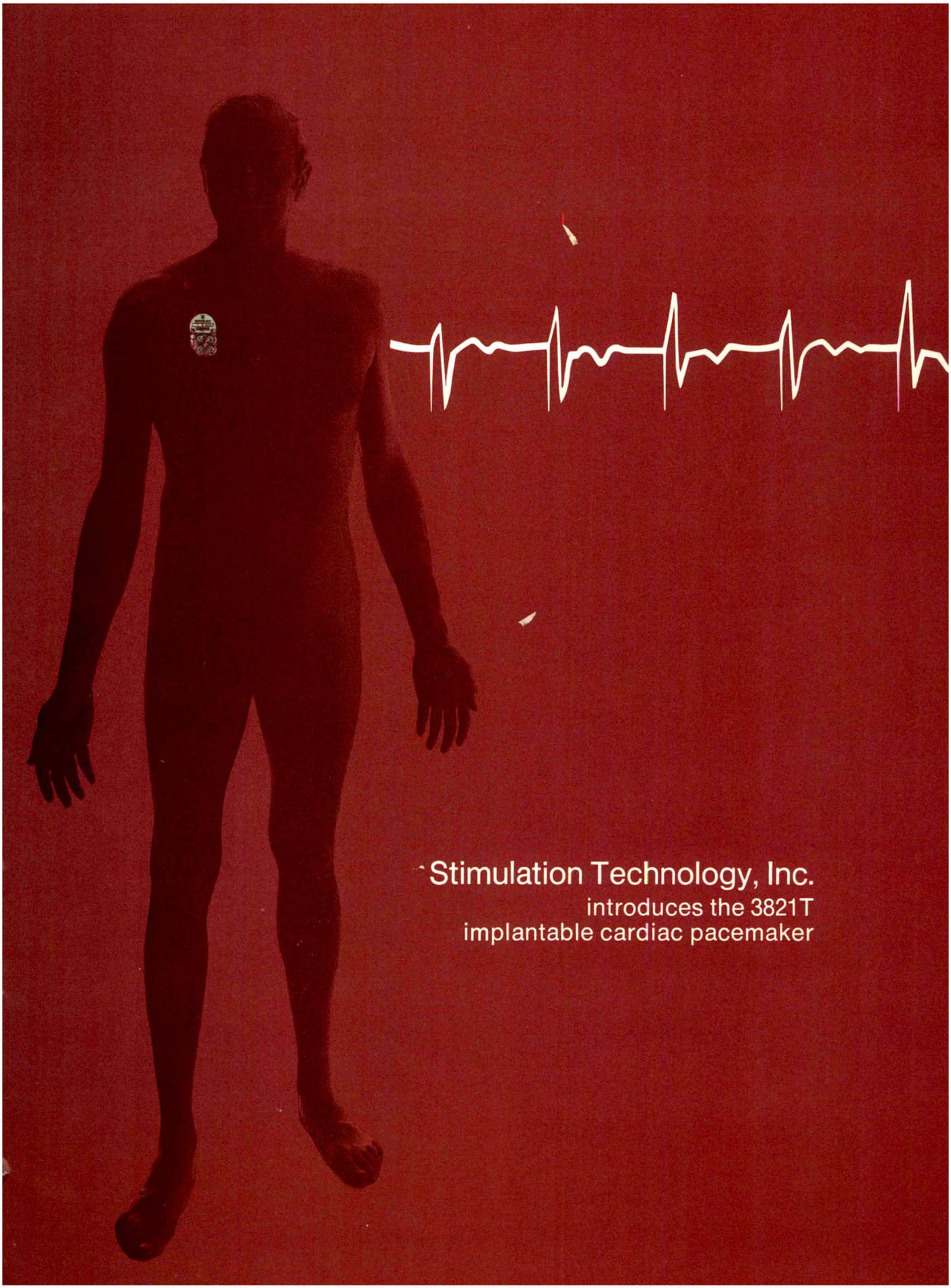

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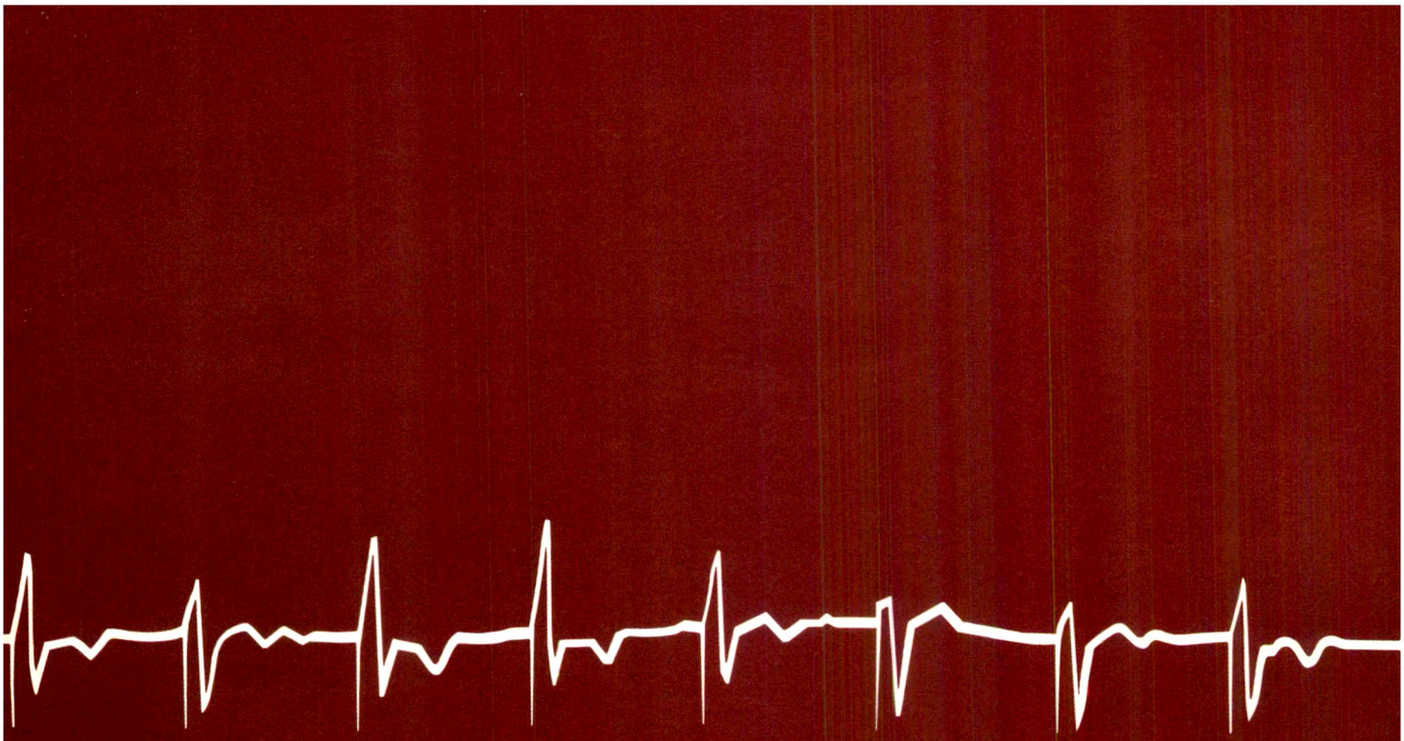

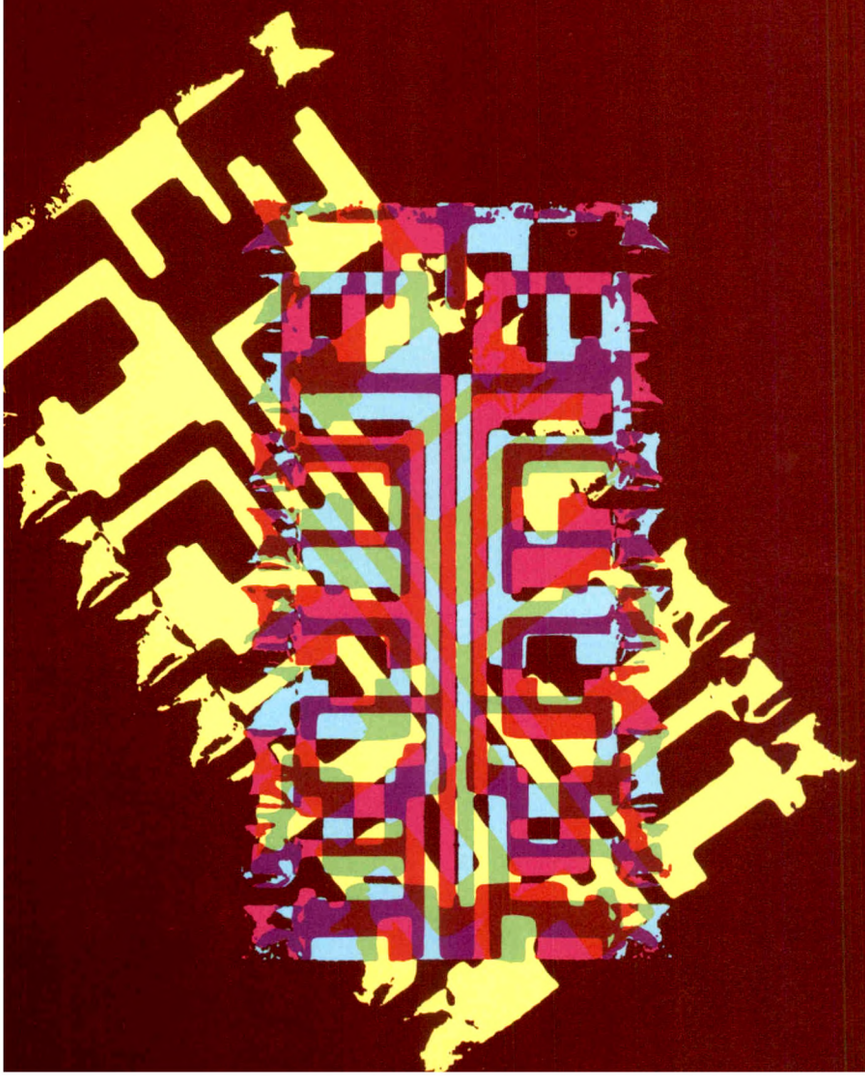

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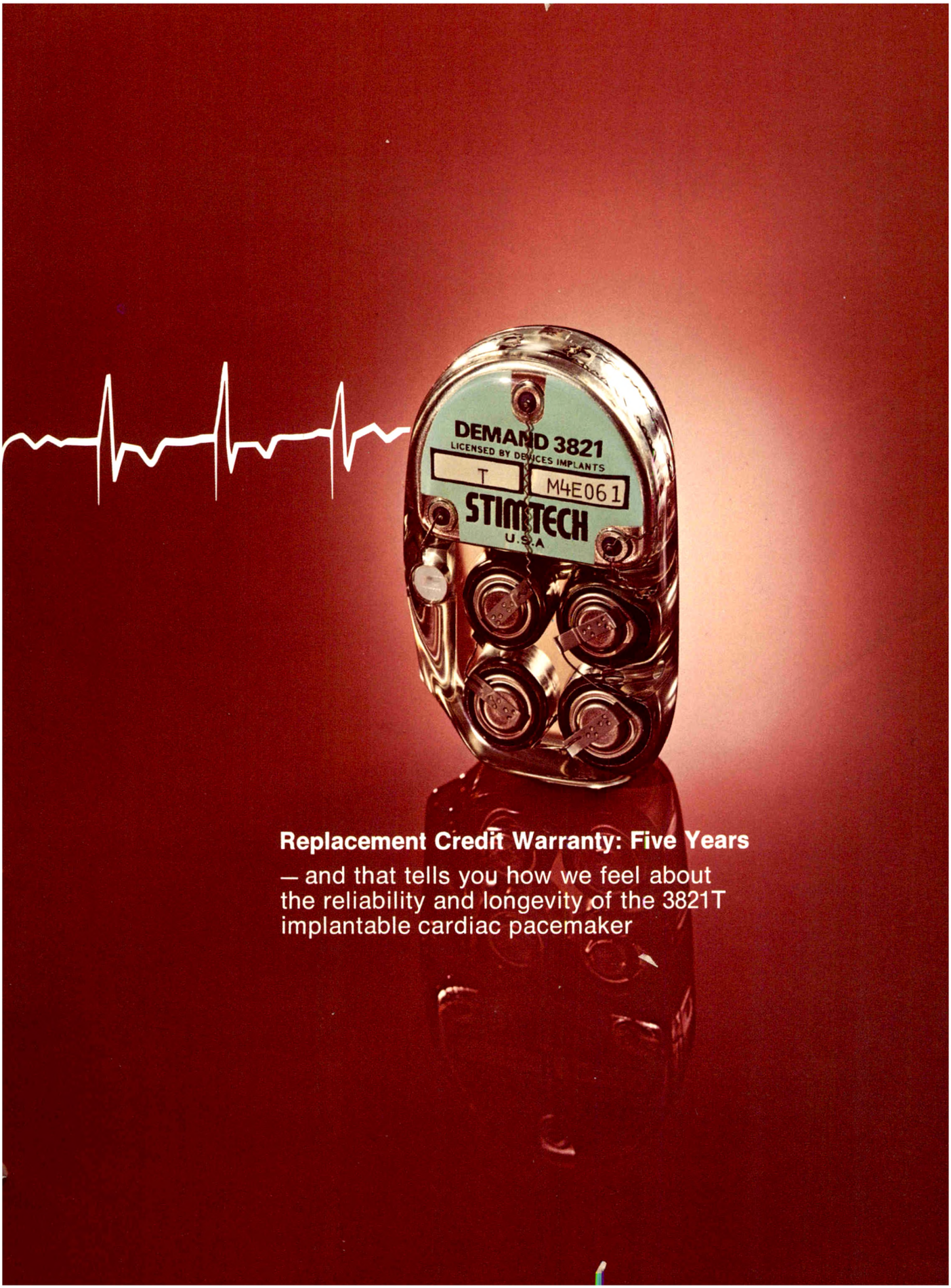

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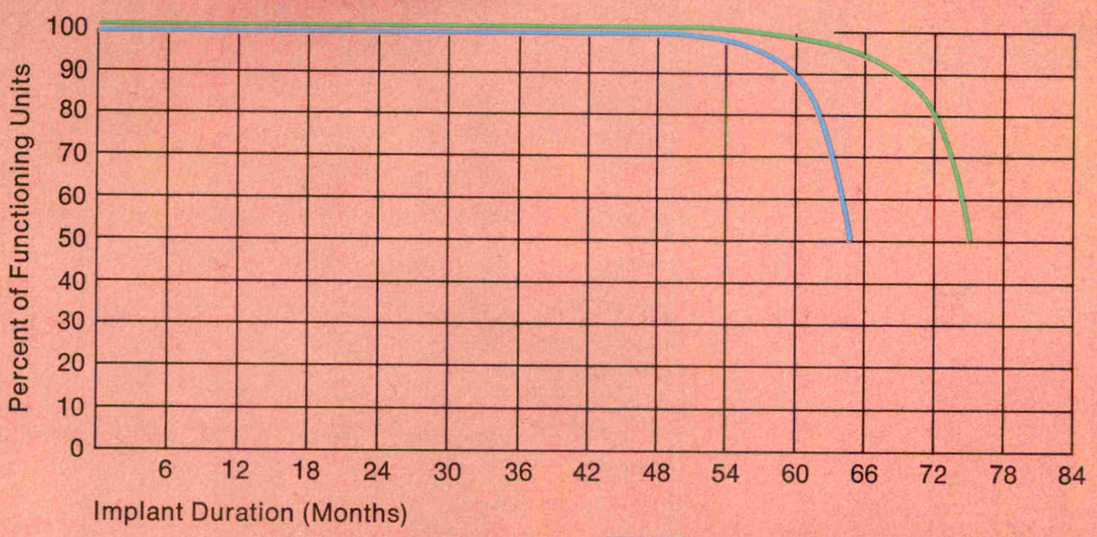

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Reticulum-Cell Sarcoma with Intracardiac Metastases

Case with Angiocardiographic Improvement After Chemotherapy

CESAR A. CONDE, MD
JOSE MELLER, MD
JOHN PANTAZOPOULOS, MD
EPHRAIM DONOSO, MD, FACC
SIMON DACK, MD, FACC

New York, New York

A case of reticulum-cell sarcoma with large intracardiac metastases was documented by cardiac catheterization and angiography. A second study after a course of chemotherapy demonstrated the palliative effects of the treatment with disappearance of the intracardiac tumor on angiocardiography. The case is discussed and a review of the literature is presented.

Primary malignant tumors of the heart are considered medical curiosities and are frequently the subject of isolated case reports; metastatic involvement of the heart is more frequently seen, especially with bronchogenic carcinoma, carcinoma of the breast, lymphoma and melanoma.[1] Among the group of lymphomas, primary and metastatic lesions of the heart have been reported, but secondary involvement is by far the more common occurence with an incidence rate of about 20 percent in the cases examined at autopsy[2]; among the three principal histologic types of lymphoma, such involvement is most common in reticulum-cell sarcoma with an incidence rate that ranges between 11 and 67 percent.[2–4]

We report a case of reticulum-cell sarcoma with extensive invasion of the heart documented electrocardiographically and angiocardiographically. Although resolution of cardiac metastasis with radiation therapy has been previously documented, this is the first time resolution of an intracardiac tumor after the use of chemotherapeutic agents has been demonstrated angiographically.

Case Report

A 66 year old Puerto Rican man was admitted to Mount Sinai Hospital on June 18, 1972 because of a left testicular mass that had been present for 2 months and had become progressively enlarged and painful. There was no significant past medical history and physical examination revealed no other abnormalities. A left orchidectomy was performed and reticulum-cell sarcoma was found on pathologic examination. Pertinent laboratory abnormalities included eosinophilia of 13 percent, erythrocyte sedimentation rate of 93 mm in 1 hour, rouleaux formation on peripheral smear and serum alkaline phosphatase of 80 units; a liver isotope scan revealed some increase in size with patchy uptake, and a liver biopsy disclosed nonspecific reactive hepatitis. The electrocardiogram revealed normal sinus rhythm at a rate of 66/min and a small q wave in leads V_1 and V_2 (Fig. 1A). The chest roentgenogram revealed an old granuloma in the periphery of the right lung; a bone X-ray survey and lymphangiogram revealed no abnormalities.

The patient remained asymptomatic and was discharged on July 13, 1972 without further treatment. He was lost to follow-up until May 1973 when he presented with pain in the upper palate of several weeks' duration. A 4 cm fungating ulceration was present in the hard palate area, and a biopsy revealed reticulum-cell sarcoma. Search yielded no evidence of metastasis elsewhere, and the patient received radiotherapy over the palate lesion with a total radiation dose of 800 rads and was discharged on June 18, 1973. One week later the palate lesion was smaller, but a 1 cm right supraclavicular node was palpated and the following week the patient was readmitted be-

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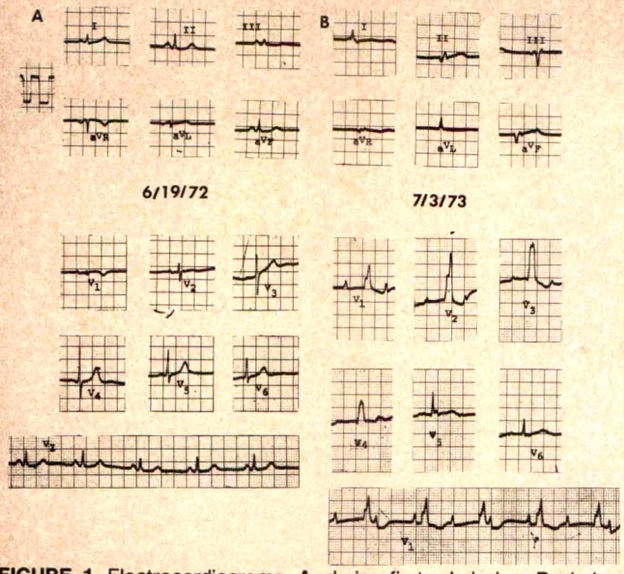

FIGURE 1. Electrocardiograms. **A,** during first admission. **B,** during second admission.

cause of the abrupt onset of mid-epigastric pain, nausea and vomiting.

On physical examination the pulse was 86/min and regular, blood pressure was 135/80 mm Hg with a paradoxical pulse of about 15 mm Hg and respiratory rate was 20/min. The neck veins were fully distended at 90° without noticeable inspiratory collapse or discernible waves. A 2 cm supraclavicular node was palpable. There was dullness on percussion over the right lung base, with decreased breath sounds. The heart sounds were distant. The abdomen was soft with the liver edge palpable 10 cm below the right costal margin, and there was mild edema of the lower legs. Venous pressure was 32 cm H_2O in the antecubital vein and 28 cm H_2O in the femoral vein. Chest roentgenogram revealed cardiomegaly and right pleural effusion. The electrocardiogram disclosed normal sinus rhythm with a prolonged P-R interval of 0.44 second, complete right bundle branch block and abnormal left axis deviation. The day after admission complete heart block developed with a junctional escape rhythm at 60/min and a QRS pattern similar to that on admission (Fig. 1B).

Cardiac catheterization and angiocardiographic findings: Right heart catheterization was performed percutaneously from the femoral vein and the catheter was

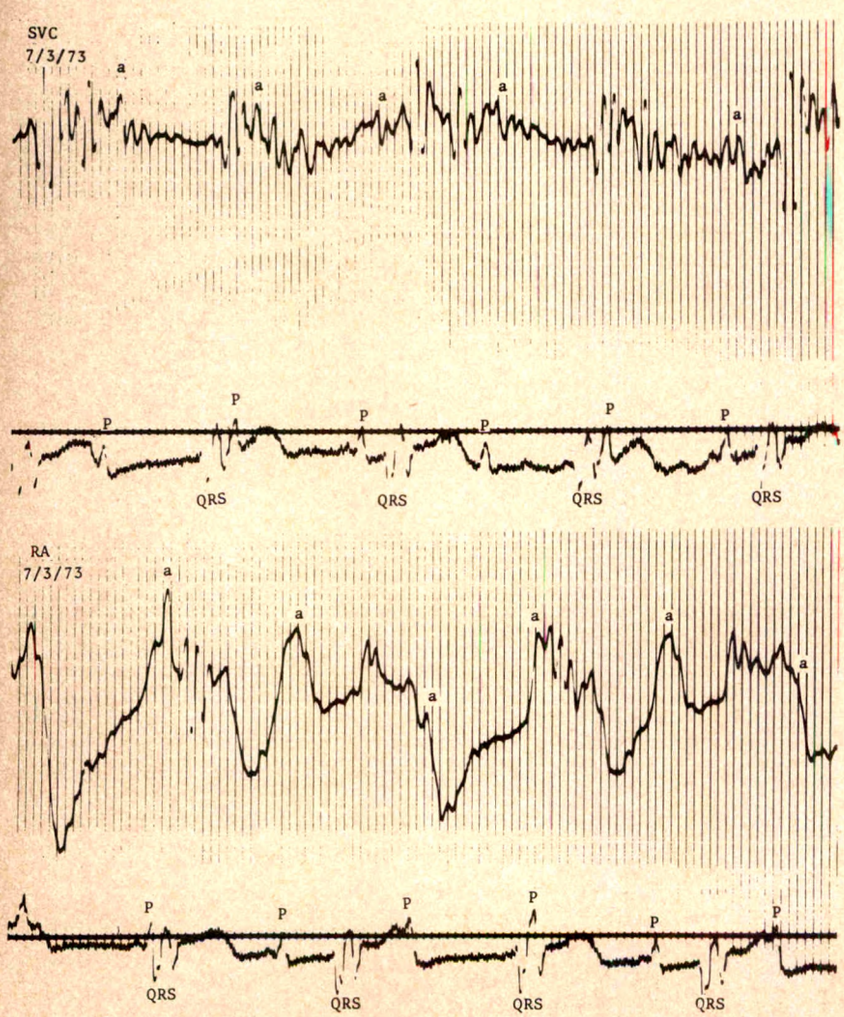

FIGURE 2. Superior vena caval and right atrial pressure tracings illustrating the poor reflection of right atrial activity into the superior vena cava. RA = right atrium; SVC = superior vena cava.

easily advanced into the right atrium, right ventricle and pulmonary artery. The pressures were as recorded in Table I. Attempts to pass the catheter tip into the superior vena cava met with difficulty in the mid and high right atrium but were successful; the pressure tracings obtained in the superior vena cava were damped and contained little reflection of right atrial wave activity (Fig. 2). Cineangiography and rapid sequence angiography of the superior vena cava and right atrium demonstrated a filling defect extending from the junction of the superior vena cava into the high and mid right atrium, leaving a channel of flow along the lateral right atrium (Fig. 3, A and B). Other filling defects were present at the level of the tricuspid valve and in the right pulmonary artery at the point of bifurcation; an increase in the thickness of the lateral wall of the right atrium suggested the presence of pericardial effusion. Bundle of His recording revealed a junctional rhythm with a normal H-V interval (45 msec). A temporary transvenous pacemaker was left in place and subsequently a permanent pacemaker was implanted.

After the angiographic diagnosis of obstructing intracardiac tumor or tumors was made, the patient was given combination chemotherapy that included prednisone, vincristine and bleomycin sulfate and he manifested good clinical improvement. Signs of peripheral neuropathy developed that were believed to be a secondary reaction to vincristine, and vinblastine was substituted. The patient was ambulatory and was discharged on a therapeutic regimen of furosemide, prednisone and allopurinol. One week later he was

TABLE I

Right Cardiac Catheterization Results

Site	Pressure (mm Hg) 7/3/73	8/22/73
Superior vena cava	(22)	(3)
Right atrium	(15)	(3)
Right ventricle	36/15	35/4
Pulmonary artery	36/17 (23)	35/14 (19)

Figures in parentheses indicate mean pressures.
PA = pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

readmitted for the fourth time because of weakness, foot pain, difficulty in walking, anorexia and dyspnea. He was debilitated, pale and tachypneic; the pulse rate was 76/min and irregular and blood pressure was 98/58 mm Hg. Cannon waves were noted in the neck veins and a murmur of tricuspid regurgitation was heard. Previous lymph node involvement and hepatomegaly were reduced. To evaluate possible regression of the intracardiac lesions, a repeat cardiac catheterization and angiography were performed. The pressures in the superior vena cava and right atrium were now within normal limits (Table I). Cannon waves were evident in both right atrial and superior vena caval pressure tracings (Fig. 4). Repeated angiocardiographic studies revealed no evidence of intracardiac tumor or pericardial

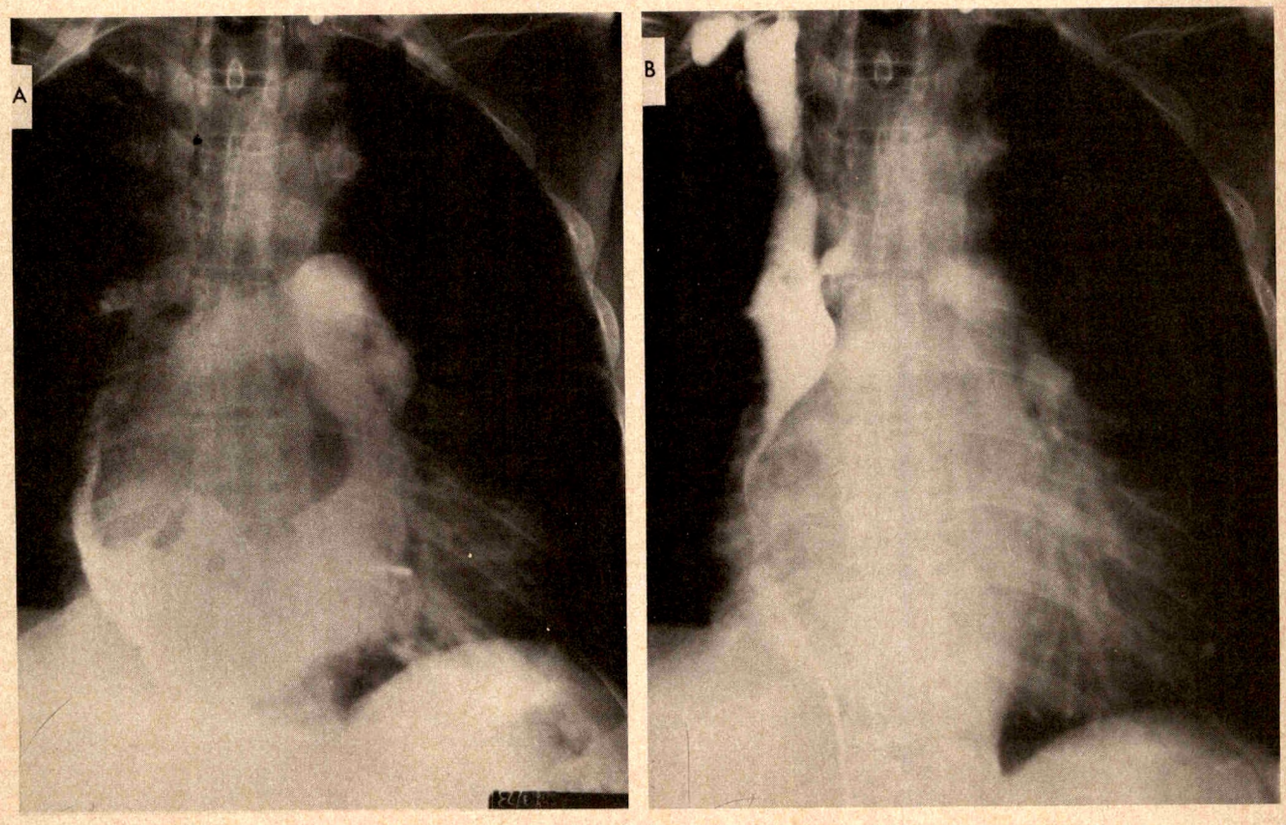

FIGURE 3. Angiocardiograms. **A,** right atrial injection, showing large intraatrial mass arising at the junction of the superior vena cava and the right atrium. **B,** superior vena caval injection showing a channel of flow along the lateral right atrium.

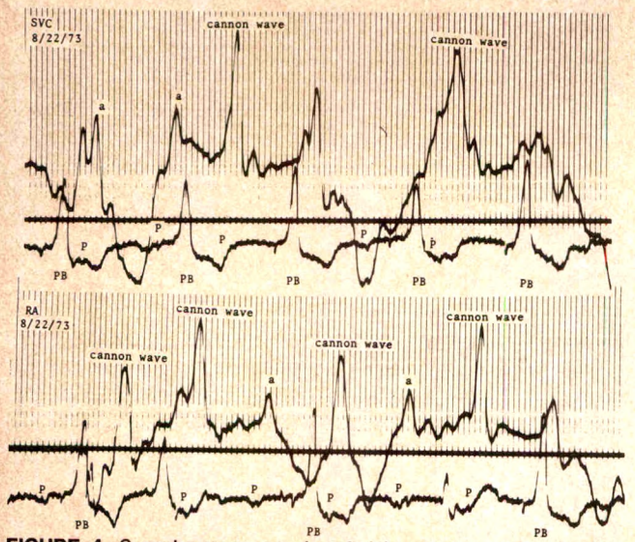

FIGURE 4. Superior vena caval and right atrial pressure tracings after treatment illustrating the good reflection of right atrial pressures into the superior vena cava and the presence of cannon waves. Abbreviations as in Figure 2.

effusion (Fig. 5). A blood transfusion resulted in marked symptomatic improvement and he was discharged. Chemotherapy was continued, but 3 months later the tumor recurred in the right testicle and the penis. The tumor responded to local radiotherapy; however, the patient's condition deteriorated and a few weeks later he was taken to the emergency room in a precomatose condition. Hypercalcemia was documented, but before any therapy was effective, he died. An autopsy was not performed.

Discussion

Our patient illustrates a case of reticulum-cell sarcoma with progressive multiorgan involvement, initially found in the testicle and subsequently in the hard palate. The condition responded well initially to local radiation therapy, but after a short period, the patient presented with signs and symptoms suggestive of superior vena caval obstruction without radiologic evidence of involvement of the mediastinal nodes. In addition, there were cardiomegaly and new conduction abnormalities that progressed from a sinus rhythm with trifascicular block to complete heart block with a junctional escape rhythm as documented by His bundle electrogram. These abnormalities were found at angiocardiography to be due to an intraatrial tumor, metastatic lesions in the pulmonary arteries and pericardial effusion.

Macroscopic lesions of this type are infrequently found in reticulum-cell sarcoma.[2,3] The electrocardiographic abnormalities recorded in our case constituted a significant clinical finding, most likely due to infiltration of the tumor at the atrial and atrioventricular (A-V) nodal levels as documented by pathologic examination in previous reports.[2,3,5,6] Arrhythmias associated with metastatic tumors of the heart have been attributed to such involvement.[5] In one specific case, it was well documented that a "sick sinus syndrome" was the presenting manifestation of reticulum-cell sarcoma invading the atrial wall and sinus node.[7] Roberts et al.[2] found that only a few of the electrocardiographic abnormalities could be explained by lymphomatous deposits in the heart and they found no cases in which there was invasion of the A-V node.

After the diagnosis was made and the extent of cardiac involvement defined, our patient was given chemotherapy and initially had a good response as manifested by regression of the lymph node enlargement and hepatomegaly, remission of the signs of superior vena caval obstruction and appearance of "cannon waves" in the neck veins when the patient's rhythm was in A-V dissociation. The latter finding suggested that the obstructive lesion, previously documented at the junction of the superior vena cava and right atrium, had decreased; otherwise it would be unlikely that waves due to atrial contraction would be transmitted to the neck. Our second study documented the complete disappearance of this intracardiac lesion; however, we did not document electrocardiographic resolution of the conduction system involvement. This suggests that although the intramyocardial involvement responded to the treatment, the neoplastic tissue was probably replaced by fibrosis, thus explaining the persistent conduction abnormalities. Although the possibility of embolization of the tumor to the lungs cannot be excluded, it is unlikely in view of the results of the second cardiac catheterization.

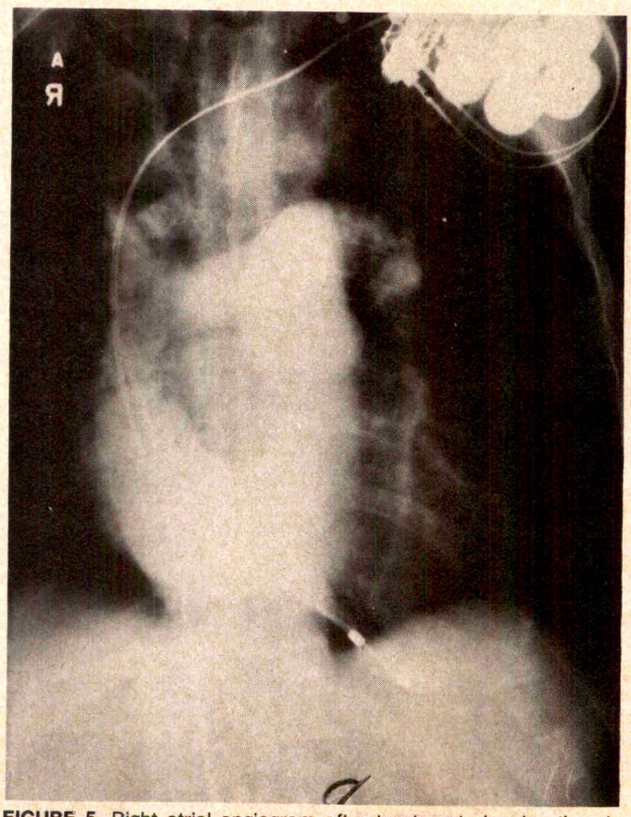

FIGURE 5. Right atrial angiogram after treatment showing the absence of intraatrial filling defects.

Review of Literature

In 1940 Shelburne and Aronson[8] reported a case of myeloblastoma (termed dural sarcoma in the original report) with cardiac metastasis, as documented by recurrent pericardial effusion and conduction abnormalities. They treated the lesion with deep roentgen therapy and demonstrated clinical improvement with disappearance of the effusion and resolution of the complete heart block. In subsequent years modern therapeutic approaches have allowed palliation,[9–11] but resolution to the degree observed in our case was not documented until 1971, when Liedtke et al.[12] reported a case of lymphosarcoma with metastasis to the pulmonary artery and pericardium and therapeutic resolution of clinical, hemodynamic and roentgenographic findings, accomplished by supervoltage radiation.

To our knowledge, ours is the first reported case of documented angiographic resolution of intracardiac lesions of reticulum-cell sarcoma after antitumor chemotherapy. The subsequent course of the patient seemed to follow the natural history of lymphomas, especially reticulum-cell sarcoma presenting as a testicular tumor, which carries a very poor prognosis.[13]

Metastatic tumors to the heart are 16 to 40 times more common than primary cardiac tumors[1] and they may originate in almost any primary malignant tumor. Cardiac involvement by metastasis is usually multiple and part of a general dissemination of the primary tumor; reported cases of solitary metastasis to the heart are extremely rare.[1,4,14–21] In absolute numbers cardiac metastases usually involve the pericardium[14–21] and occur most frequently in bronchogenic carcinoma and carcinoma of the breast, being found in up to one third of these cases. Glancy and Roberts[22] reported a 64 percent incidence rate of cardiac metastases in patients who died of malignant melanoma; the more frequent location was the myocardium rather than the epicardium, but the metastases did not seem to cause dysfunction unless the cardiac involvement by the tumor was extensive. Roberts et al.[23] also reported a 37 percent incidence rate of leukemic infiltrates and 54 percent incidence rate of focal cardiac hemorrhages in necropsy examination of patients with acute leukemia. There were usually few of these abnormalities; they were most frequently located in the pericardium and walls of the left ventricle and right atrium, only occasionally extending through the entire cardiac wall and rarely producing clinically detectable signs or symptoms.

Cardiac metastases are found in 20 percent of the cases of malignant lymphoma examined at autopsy[2]; they are most common in reticulum-cell sarcoma; however, the incidence rates in different series range from 11 to 67 percent.[2–4,24] In Madiano and Sokal's series[3] the myocardium was more frequently involved than the pericardium and only four patients had isolated pericardial lesions; when the pericardium was involved gross lesions were frequently seen but, like Roberts et al.,[2] they found that the majority of lesions in the myocardium, including the epicardium, were microscopic. Roberts et al.[2] reported that the most frequent site of involvement was the visceral pericardium and only one patient had a tumor in a cardiac valve (tricuspid); in at least nine subjects tumor nodules extended through the entire wall of a cardiac chamber or through the atrial septum; however, cardiac rupture secondary to metastatic lymphoma is rare[25] and in no subject did it involve the A-V node or bundle. Cardiac symptoms depended on the location of the metastasis and were present in less than 10 percent of the cases, but symptoms that are often attributed to cardiac involvement are not always the result of lymphoma of the heart.[2] None of the patients with reticulum-cell sarcoma in Roberts' series had signs or symptoms of cardiac dysfunction that could justifiably be attributed to lymphoma involving the heart.

Endocardial or valvular metastatic tumors are unusual since these areas are relatively avascular; they probably occur by direct implantation, usually on an abnormal endothelium.[1,16] In 1955 Brucker and Glassy[26] reviewed the literature on primary reticulum-cell sarcoma of the heart and found that 16 percent of the 43 patients presented with a superior vena caval syndrome and 37 percent had hemopericardium. Although these patients were considered to have primary reticulum-cell sarcoma,[26,27] several had postmortem or surgical evidence of involvement of other organs.

The clinical presentation of our case and its course illustrates the poor prognosis of patients with disseminated reticulum-cell sarcoma, despite the palliative effects of antitumor chemotherapy and subsequent radiotherapy.

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Echocardiographic Diagnosis of Right Atrial Extension of Wilms' Tumor

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A fourth case is presented of propagation of Wilms' tumor to the right atrium through the inferior vena cava. Ultrasonic examination of the heart was diagnostic of the tumor and the diagnosis was confirmed by angiographic studies and surgical exploration. This report provides the first echocardiographic description of a right atrial tumor in a child.

Tumors of the heart may mimic a great variety of cardiovascular diseases. We report a case of a tumor in the right atrium that mimicked renal disease.

Case Report

A 5 year old black girl was referred to this hospital because of an abdominal mass, ascites and pedal edema. She had had intermittent vague abdominal pain associated with anorexia for 3 to 4 months. Three weeks before admission, she was examined by a physician for repetitive vomiting. Ascites and hepatomegaly were noticed and she was admitted to a local hospital. Despite anorexia, she had gained 3.5 kg since the onset of her symptoms. Because an intravenous pyelogram revealed a nonfunctioning left kidney, the patient was referred to this hospital.

On examination, she was found to be alert, oriented, slightly pale and in no respiratory distress. There was marked pitting edema of the legs and severe abdominal distension. The liver was felt 10 cm below the right costal margin. A vague mass was felt in the left flank. The neck veins were markedly dilated with prominent *a* waves. The arterial pulses were normal. The blood pressure was 132/80 mm Hg in the right arm. The precordium was hyperactive in the region of the left lower sternal border. The first heart sound was loud and split; the second sound was normally split and its pulmonary component was soft. A low-pitched grade 2/6 midsystolic ejection murmur was heard along the left lower sternal border. A grade 2/6 presystolic murmur was also present and was well localized to the tricuspid area. No systolic ejection or early diastolic sounds were audible.

A chest roentgenogram (Fig. 1) revealed moderate cardiac enlargement (cardiothoracic ratio 0.6), normal arterial and venous vascularity, a left aortic arch and dilated azygous vein shadow.

An electrocardiogram (Fig. 2) revealed sinus rhythm with a mean frontal axis of approximately +110°, a P-R interval of 0.14 second, a qR pattern in leads V_4R to V_3R, an rs pattern in lead V_1, a qR pattern in lead V_6 and a 26 mm deep S wave in lead V_2.

A phonocardiogram (Fig. 3) over the tricuspid area revealed a split first heart sound, a midsystolic murmur and a presystolic murmur.

A liver scan was reported to show normal findings. The skeletal survey included roentgenograms of the skull and limbs, and no destructive lesions were seen. An intravenous pyelogram revealed normal appearance of the right kidney but no opacification of the left kidney. A cystogram was interpreted as normal.

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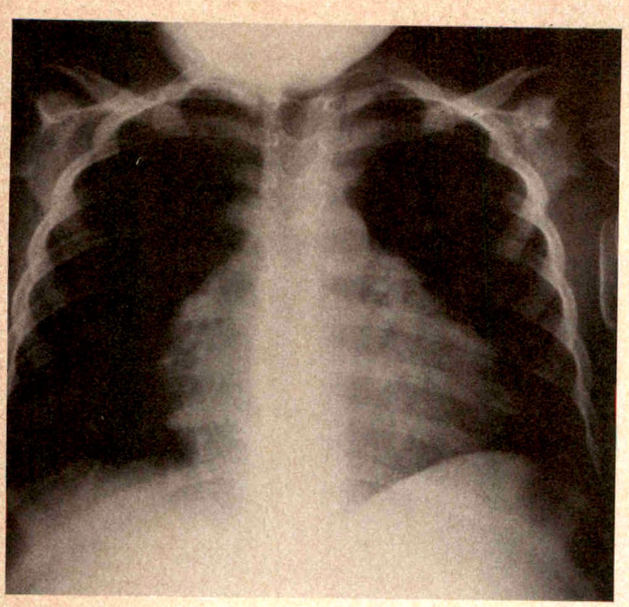

FIGURE 1. Chest roentgenogram, frontal view. Note the prominent azygos vein shadow.

Echocardiography

Ultrasonic examination was performed with a 5 megahertz nonfocused transducer, Ekoline 20, and a Cambridge strip chart recorder using the well established technique of echocardiographic examination in children.[1,2] The mitral valve was first located and then the transducer was rotated toward the aortic and the tricuspid valves. Figure 4 shows the relative dimensions of the right and the left ventricles. The transducer was then rotated upward to record the outflow tracts and the left atrium. The ventricular septal motion and thickness were normal. Figure 5 shows that as the transducer was rotated toward the right atrium, an abnormal pattern of echoes was seen posterior to the anterior tricuspid leaflet. The region of the right atrium behind the anterior cusp of the tricuspid valve is normally an echo-free space.[2] However, dense echoes were seen in the right atrial region adjacent to the anterior tricuspid leaflet. As the transducer was rotated farther to the right and downward (Fig. 6), the right atrial cavity was totally filled with abnormal echoes that projected anteriorly in late diastole. There was no evidence of tricuspid stenosis (ejection fraction slope 110 mm/sec, amplitude of anterior tricuspid leaflet motion 18 mm). The diagnosis of right atrial tumor was made on the basis of these echocardiographic findings.

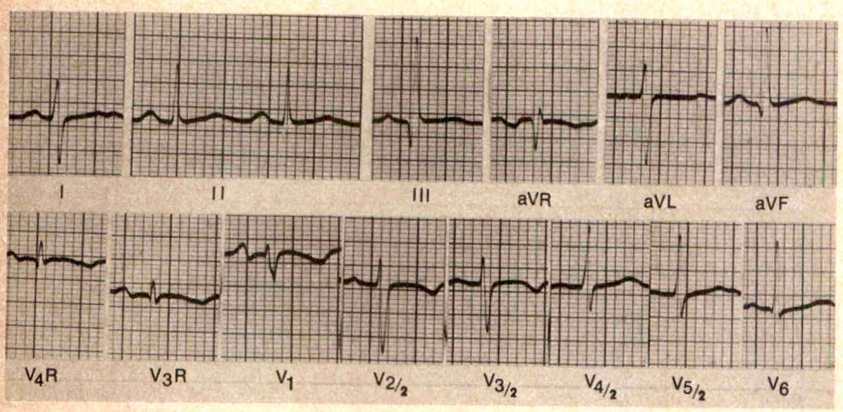

FIGURE 2. Electrocardiogram.

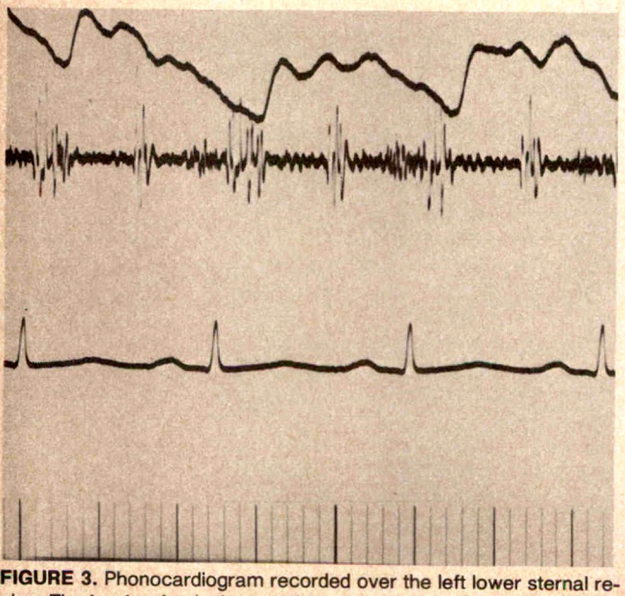

FIGURE 3. Phonocardiogram recorded over the left lower sternal region. The **top tracing** is the carotid pulse.

Cardiac Catheterization and Angiography

These procedures were performed on the 3rd hospital day. The catheter was passed through the right basilic vein to the right atrium. The right ventricle and the inferior vena cava were entered with difficulty. The catheter could not be advanced into the inferior vena cava beyond the entry of the hepatic veins. The pulmonary artery could not be entered. The pressures recorded (in mm Hg) were as follows: right atrium 20/10 (mean = 15, a = 20, v = 18), right ventricle 21/0–4 (mean = 16). A biplane right atrial cineangiogram (Fig. 7) revealed a large rounded mobile mass that filled 40 per cent of the right atrial cavity. The mass moved toward the tricuspid valve in late diastole. The levophase was normal. A right ventricular injection revealed no tricuspid insufficiency, and no tumor was seen in the right ventricle. An injection near the inferior vena cava-right atrial junction revealed obliteration of the inferior vena cava and reflux of the contrast medium into the dilated hepatic veins.

The catheter was then passed by way of the right brachial artery into the upper abdominal aorta, and injection of contrast medium demonstrated a left renal artery supplying a large left renal mass. There was evidence of

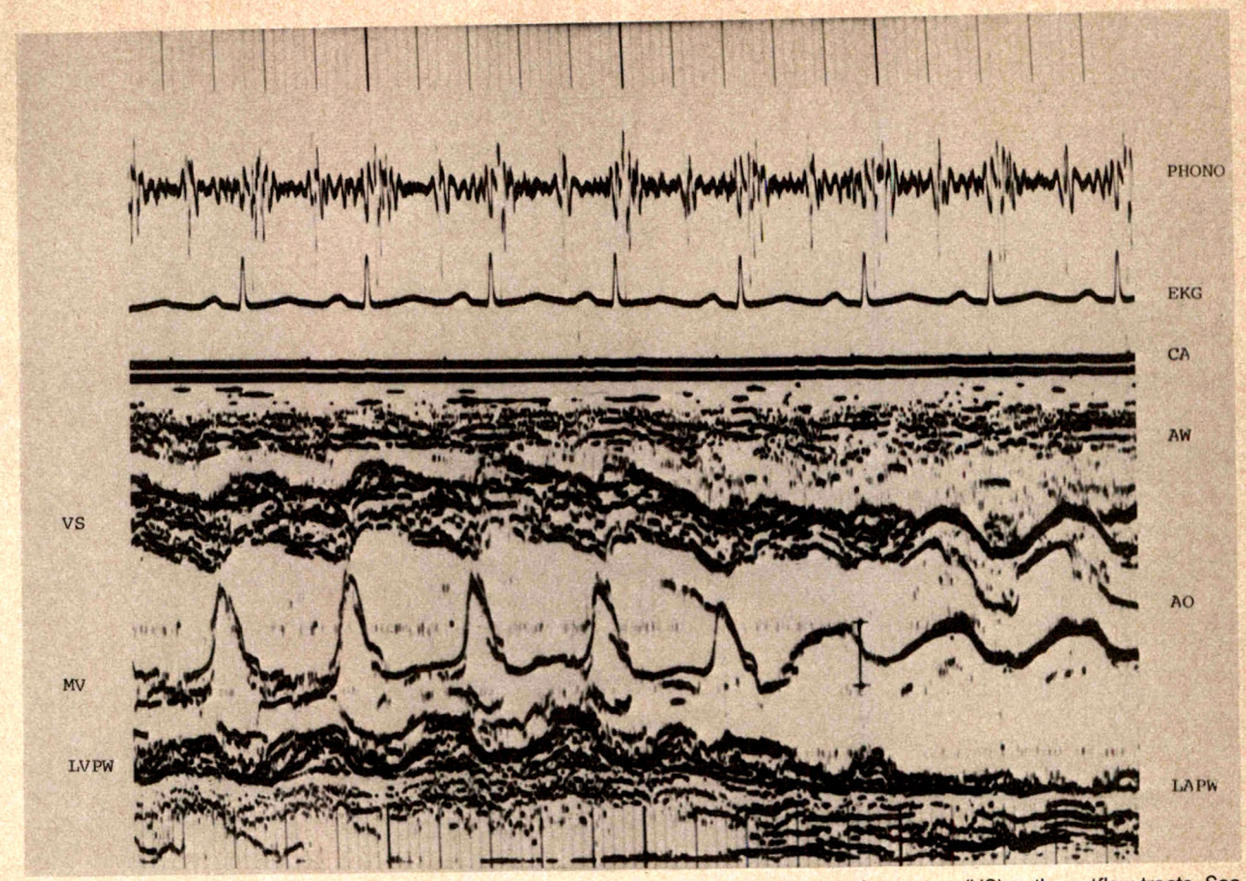

FIGURE 4. Echocardiogram shows the absence of any tumor echoes in the region of the ventricular septum (VS) or the outflow tracts. See text for details. AO = aorta; AW = anterior heart wall; CA = crystal artifact; LAPW = left atrial posterior wall; LVPW = left ventricular posterior wall; MV = mitral valve.

neovascularization in the region of the left kidney, and massive arteriovenous shunting resulted in dense opacification of dilated veins extending from the tumor toward the liver. An injection was made in the right iliac vein, by way of the saphenous vein, and total blockage of the inferior vena cava was seen at the level of the right renal vein. There was drainage into the Batson's paravertebral plexus, which emptied into the superior vena cava by way of the azygos system.

Clinical Course

On the 5th hospital day, a laparotomy revealed that a large tumor of the left kidney had extended to the retroperitoneum, mesocolon and liver. The tumor was also seen to invade the inferior vena cava and to extend to the caval-atrial junction. A liver biopsy confirmed the hepatic lesions to be metastatic nephroblastoma. The abdominal tumor was judged nonresectable, and the plans to remove the atrial portion of the tumor were abandoned. The patient was treated with actinomycin-D and radiotherapy. On the 18th hospital day, her condition suddenly deteriorated and she died in a state of low cardiac output. Permission to perform an autopsy was denied.

Discussion

Wilms' tumor of the kidney has been reported to extend directly to the right atrium through the inferior vena cava.[3–6] The right atrial extension of the tumor was not diagnosed clinically in three previously reported cases,[4–6] and was not appreciated even with right atrial angiography,[6] becoming obvious only at autopsy. Echocardiography is of proved value in the detection of cardiac tumors,[7,8] including the most widely studied tumor of the heart, atrial myxoma.[9–12] The majority of atrial myxomas occur in adults, and 75 percent are found in the left atrium. Review of the literature revealed only five ultrasonic descriptions of right atrial tumors, all of myxomas in adults.[7,13–16] Our case is reported because (1) it is rare for Wilms' tumor to propagate intravascularly to the right side of the heart, and (2) the diagnosis of right atrial tumor was by echocardiography and then confirmed by angiography and surgical exploration.

Review of the five reported cases of right atrial myxoma studied by ultrasound reveals some interesting features. Four of these reports describe only the echoes related to the ventricular prolapse of the tumor.[7,13,15,16] One report describes the tricuspid valve echoes in relation to the right atrial tumor echoes, but because the published photograph is of poor quality, it is impossible to analyze the tricuspid valve data.[14] It is easier than in adults to record the tricuspid valve in normal infants and children, for whom the technique of right atrial echocardiography is well established.[2]

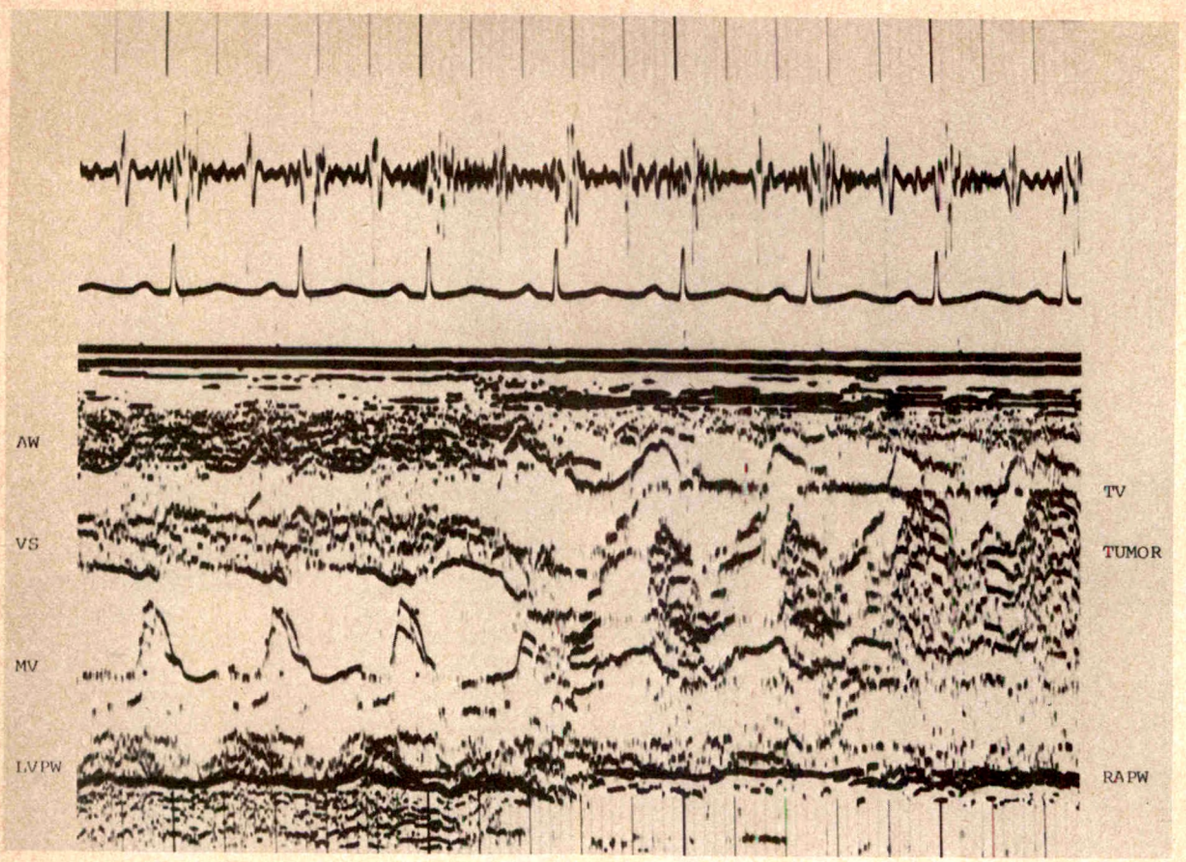

FIGURE 5. Echocardiogram of the right atrial region. See text for details. RAPW = right atrial posterior wall; TV = tricuspid valve.

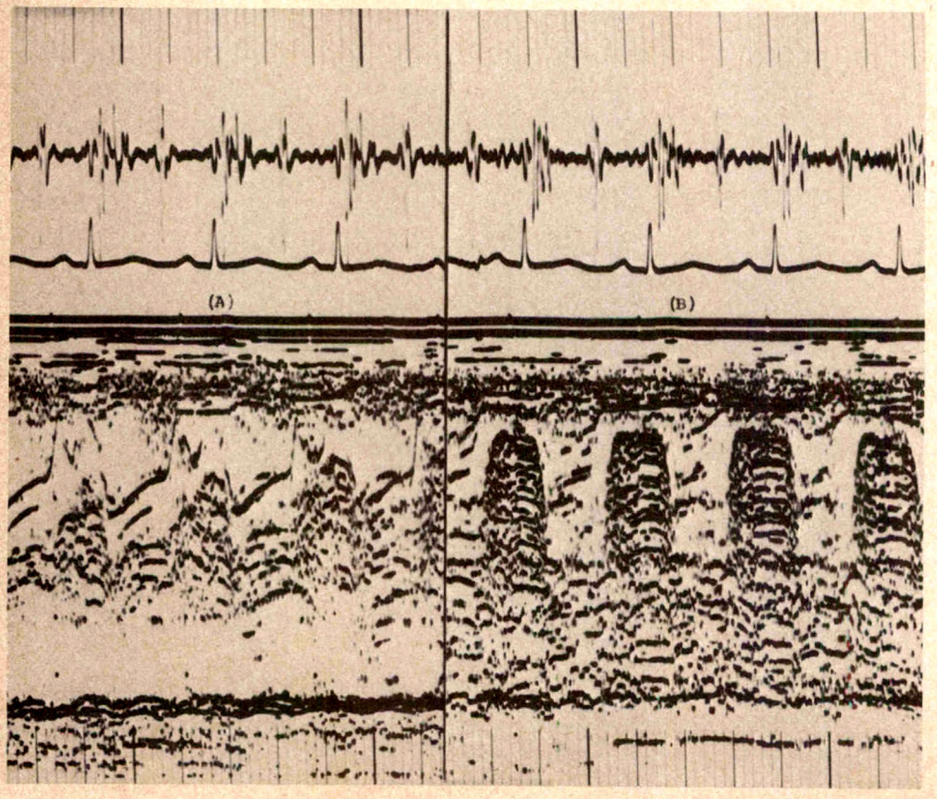

FIGURE 6. Echocardiogram of the tricuspid valve **(A)** and of the motion of the tumor anteriorly toward the tricuspid valve **(B).** See text for details.

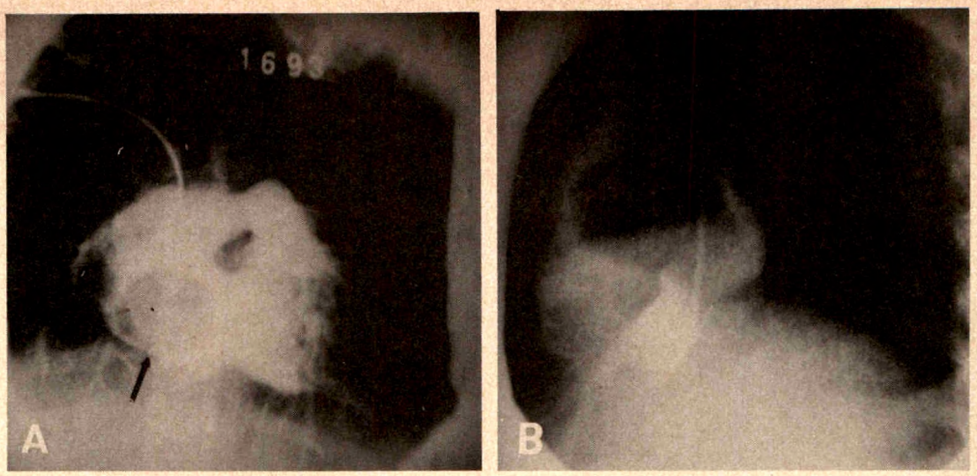

FIGURE 7. Selected frames from the biplane cineangiograms. **A,** anteroposterior view showing large rounded radiolucent density in the right atrial region **(arrow). B,** lateral view. Inferior vena caval injection outlines the anteroposterior extent of the mass.

The right atrial echocardiogram (Fig. 6) of our patient shows a dense layer of abnormal echoes, most prominent in the posteroinferior portion of the right atrium. As the transducer was rotated from the mitral valve region toward the right atrium (Fig. 5), the anterior leaflet of the tricuspid valve could be recorded in systole as well as in diastole. However, at this level the tumor echoes were minimal (Fig. 6A). As the transducer was rotated farther to the right and posteroinferiorly, anterior tricuspid leaflet echoes became smaller in amplitude, but a dense layer of tumor echoes completely filled the right atrial cavity (Fig. 6B). Angiographically, the tumor was very mobile, moving toward the tricuspid orifice in mid- and late diastole. This motion was also seen in the ultrasonic study (Fig. 6B). We conclude that the tumor moved anteriorly, leftward and downward (that is, from the inferior vena caval junction toward the tricuspid orifice) during diastasis and the last rapid filling phase of the right ventricle without actually entering the right ventricular cavity.

Our case differs from the three reported cases of Wilms' tumor with direct extension to the right atrium in that there was invasion of the surrounding structures and the tumor metastasized to the liver. Murphy et al.[5] were able to remove the tumor thrombus from the right atrium and their patient was free of recurrence 3 1/2 years postoperatively.

In conclusion, we believe that greater use of echocardiography may permit more frequent and, one hopes, earlier detection of tumors of the heart.

Acknowledgment

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SYMPOSIUM
Reperfusion During Acute Myocardial Infarction. Part II

Eliot Corday, MD, FACC and Samuel Meerbaum, PhD, FACC, *Guest Editors*

Revascularization After 3 Hours of Coronary Arterial Occlusion: Effects on Regional Cardiac Metabolic Function and Infarct Size

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Two experimental series of closed chest dogs were compared: Group A (five dogs with 7 days of continuous occlusion of the proximal left anterior descending coronary artery); and Group B (six dogs with 7 days of reperfusion after 3 hours of acute occlusion of the same artery). Hemodynamic measurements, ventricular wall motion, coronary sinus blood flow and regional metabolism in both coronary occluded and nonoccluded segments of the left ventricle were measured sequentially. The infarct size was characterized by detailed histopathologic analysis.

In the control dogs (Group A), mechanical and metabolic function remained severely depressed after 7 days of occlusion, and mean infarct size was 31.6 percent. In Group B, significant mechanical and metabolic dysfunction developed during 3 hours of occlusion and did not improve during the 1st hour of reperfusion. However, after 7 days of reperfusion, function returned to near preocclusion level. Mean infarct size was 14.2 percent, but in two of the six dogs infarct size was 43 percent and 23 percent, respectively.

The study confirmed the unstable character of the early phase of reperfusion, attributed to cell swelling, edema and hemorrhages that resulted in inadequate coronary reflow, arrhythmias and functional derangements. Prolonged reperfusion for 7 days reduced mean infarct size and improved cardiac function.

Considerable debate is focused on whether coronary bypass surgery after coronary occlusion can save jeopardized myocardium and reduce mortality. Differing results have been reported for revascularization applied after occlusion, ranging from striking benefits to harmful effects and unacceptable mortality.[1–5] Specifically, questions are raised whether reperfusion after an acute coronary occlusion is capable of reducing infarct size and restoring regional mechanical and metabolic function of the heart. Time limits of myocardial viability have been postulated which, if transferred to man, would restrict successful revascularization to the earliest interval of acute ischemia.[6] Clarification is sought about functional derangements, hemorrhages and accelerated necrosis observed after reperfusion.[7,8] Such questions and conflicting reports emphasize the need for further controlled investigations aimed at elucidating the effects of reperfusion on function and myocardial morphologic features of occluded and nonoccluded regions of the heart after specific periods of coronary occlusion.

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Clinical experience must, of course, provide the ultimate answers, but investigations in man do not lend themselves to preocclusion control studies and prohibit necessary extensive measurements. Interpretation of comprehensive data from animal experimentation might help resolve the important and controversial clinical issues concerning revascularization during acute myocardial infarction. Development of new experimental animal models now permits simultaneous measurement of regional left ventricular mechanics, metabolism and electrophysiology, coupled with detailed study of pathophysiology.[9] Several reperfusion studies have been performed in open chest preparations or in closed chest animals previously subjected to thoracotomy for the purpose of implanting coronary occluders and various instruments.[10] These models are subject to criticism because they may cause physiologic distortions or provide insufficiently detailed measurements. Our own experience indicates that cardiac function is often significantly depressed in the open chest preparation and that it is difficult to maintain satisfactory performance of previously implanted devices.

One of the fundamental questions relates to the maximal period of time after an acute coronary occlusion when myocardial dysfunction can still be reversed, viability maintained and infarct size minimized by reperfusion. For this investigation we chose the 3 hour period of occlusion on the basis of prior indications that in the dog this may represent the limit beyond which extensive irreversible myocardial damage might be expected.[7,11] In addition, 3 hours appears to be a minimal time required for preparing a hospitalized patient for coronary bypass revascularization surgery.

Prior experimental studies that generally involved brief periods of reperfusion after coronary occlusion revealed development of reperfusion arrhythmias, hemorrhagic infarction and abnormal metabolic and mechanical responses in the ischemic and nonischemic myocardium. Our recent study[12] of 3 hours of occlusion of the left anterior descending coronary artery followed by 5 hours of reperfusion clearly indicated the functionally unstable character of the early reperfusion period.

This study was aimed at comparing the effects of early (1 hour) and prolonged (7 day) reperfusion after 3 hours of total occlusion of the proximal left anterior descending coronary artery. We employed an experimental closed chest intracoronary balloon occlusion-reperfusion model,[9] which obviates thoracotomy and eliminates recuperation periods normally required with implanted preparations. The new model provides simultaneous electrocardiographic, hemodynamic, regional myocardial mechanical and metabolic measurements at regular intervals before and after coronary arterial occlusion and subsequent reperfusion. Regional metabolic function was monitored in both occluded and nonoccluded segments of the left ventricle. Hemodynamic indexes of mechanical function, segmental left ventricular kinesis and ejection fraction were assessed. Emphasis was placed on detailed histopathologic analysis to define the extent and distribution of myocardial infarcts resulting from 3 hours of coronary occlusion followed by 7 days of reperfusion. All the data were compared with similar measurements in a control series in which coronary occlusion was maintained over a period of 7 days.

Methodology

Experimental Procedure

Experiments were carried out in 62 closed chest anesthetized dogs weighing 30 to 35 kg. Five dogs were excluded after profound cardiac shock developed. The present study encompassed 57 dogs. There were two groups with identical aseptic preparation in the control period and a subsequent 3 hour period of intracoronary balloon occlusion of the proximal left anterior descending coronary artery. Seventeen dogs died during the period of occlusion; the remaining 40 animals were subdivided into Groups A and B. In Group A (21 dogs) occlusion was maintained for 7 days, whereas in Group B (19 dogs) deflation of the intracoronary balloon after 3 hours of coronary occlusion provided a reperfusion period extending to 7 days. Surviving dogs in both groups were restudied on the 7th day, and the hearts were then excised for histopathologic analysis.

The dogs were initially anesthetized with morphine (2 mg/kg body weight intramuscularly) and, 20 to 30 minutes later, with pentobarbital sodium (15 mg/kg intravenously). During the first 4 hours supplemental doses were administered as necessary to maintain a state of light anesthesia.

A Harvard respirator provided artificial respiration through a cuffed endotracheal tube. An initial dose of heparin (5 mg/kg) was administered, and further doses of 3 mg/kg were given at 1 hour intervals during the experiment, up to 4 hours after the coronary occlusion. Subsequently, heparin was administered at 8 hour intervals. During the initial 4 hours, fluid loss was estimated and replaced by infusion of physiologic saline solution at a rate of 75 to 100 cc/hour. After 4 hours of occlusion in Group A, and 3 hours of occlusion plus 1 hour of reperfusion in Group B, all instrumentation and catheters were removed from the dogs (except for the balloon occlusion intracoronary catheter in Group A). After appropriate treatment of incisions, the dogs were moved to the vivarium where they were observed over the next 7 days. On the 7th day, the dogs were lightly reanesthetized and fully instrumented, and experimental determinations were carried out in the same manner as during the initial period of occlusion. Subsequently, the dogs were killed by an overdose of pentobarbital sodium and the heart was removed for gross inspection and detailed histopathologic study.

Instrumentation

A single lumen balloon catheter was used for local occlusion of the left anterior descending coronary artery. The intracoronary catheter was maneuvered under fluoroscopic control through an angiographic cannula temporarily positioned in the left coronary artery. The catheter was located at the desired site and its balloon inflated with Hypaque® sodium 50 percent (weight/volume) to permit observation of the exact location of the occlusion and to control the extent of the balloon inflation. Deflation of this balloon resulted in reperfusion of the previously occluded coronary artery. Although the anatomy of the coronary arteries var-

ied from dog to dog, an effort was made in each case to place the occlusion in the proximal left anterior descending artery immediately distal to its first diagonal branch.

A Ganz thermodilution catheter was placed in the coronary sinus for measurement of coronary sinus flow[13] as well as blood sampling. A no. 4F double lumen balloon catheter was advanced through or alongside the larger coronary sinus cannula and deep into the great cardiac vein until its open tip was located deep within the anterior interventricular coronary vein. In this manner, the center lumen of this balloon catheter allowed collection of blood from the coronary vein draining the ischemic region. Before sampling, the balloon of the catheter in the great cardiac vein was inflated for 10 to 15 seconds to facilitate separation of venous compartments. Blood sampled from the coronary sinus during inflation of the balloon represented venous drainage from the nonoccluded segment of the left ventricle. Metabolic measurement and checks with dyes corroborated very significant and almost total separation of the coronary occluded and nonoccluded zone venous compartments. It was therefore possible to obtain regional measurements of oxygen extraction as well as lactate and potassium balance from both the ischemic and nonischemic myocardial zones. Repeat coronary arteriography was performed to check on the completeness of the coronary occlusion and reperfusion.

Hemodynamic and Metabolic Measurements

Heart rate and cardiac rhythms were determined from precordial electrograms (lead V_4). A catheter tip transducer (BioTech Instruments) was passed from the right femoral artery into the left ventricle to provide high fidelity measurement of left ventricular systolic pressure and end-diastolic pressure. The maximal rate of left ventricular pressure rise (dP/dt) was obtained by means of electrical differentiation. A Statham P23Db pressure transducer connected to a catheter passed through the left femoral artery was used to measure aortic root pressure and specifically peak systolic pressure. Left ventriculography was performed during the control period, at the end of the 3 hours of coronary occlusion, after 1 hour of reperfusion and after 7 days of occlusion or reperfusion. Left ventricular ejection fraction was calculated from peak systolic and end-diastolic serial cineventriculographic frames. Cardiac output was determined by the thermodilution method using Swan-Ganz catheters. Stroke work and systemic vascular resistance were derived from this determination. Total coronary sinus blood flow was determined by the Ganz thermodilution technique.

In both groups, control measurements were obtained twice during a 30 minute stabilization period before balloon occlusion of the left anterior descending coronary artery. Hemodynamic measurements were then performed at 30 minutes and at hourly intervals until 3 hours after the occlusion and 1 hour after reperfusion in Group B. These measurements were repeated on the 7th day. Blood sampling for myocardial oxygen, lactate and potassium balances was also carried out at these intervals, as well as at 5 minutes after occlusion (both groups) and at 5 minutes after reperfusion (Group B).

Lactate levels were determined by the Hans-Jurgens-Hohorst technique,[14] and potassium levels by means of flame photography. Blood gases (partial pressures of oxygen [PO_2] and carbon dioxide [PCO_2]) as well as pH were monitored throughout the experiment. Hemoglobin and oxygen saturation were measured.

All hemodynamic and electrographic data were recorded on an Electronics for Medicine model DR-16 recorder at paper speeds of 50 and 100 mm/sec. Statistical results of measurements are expressed as mean ± standard error of the mean. Significance was computed by means of the paired t test.

Histopathology

After 7 days of occlusion (Group A) or 7 days of reperfusion (Group B), gross and microscopic examinations were performed in the excised hearts to assess the extent of myocardial damage and to determine the histopathologic correlates of occlusion and reperfusion, respectively. The anterior and posterior aspects were photographed before and after neutral buffered formalin fixation. The heart was cut vertically through the left ventricular wall, posteriorly along the septum. The left chamber was gently cleaned of postmortally clotted and liquid blood to examine and photograph the posterior and anterior endocardium. All heart chambers were cleared of liquid and clotted blood, the heart weighed and then immersed in saline solution to measure its volume in milliliters. An average of ten 5 to 7 mm thick parallel slabs were cut perpendicular to the left anterior descending artery and photographed.[15]

The grossly visible infarct size was estimated by discoloration and textural alteration. The thickness of each slab was recorded. Alternate slabs were circumferentially sampled by means of a 3 to 4 mm thick subslab, representing both the right and left sides of the heart, and analyzed microscopically, using hematoxylin-eosin stains. Arterial alterations were further studied by the Van Giesen elastica stain. Gram stains were employed where infection was noted. The infarcts were delineated microscopically and recorded on square millimeter paper. Computation of infarct size was achieved by a total square count of millimeters infarcted, multiplied by the actual slab thickness in millimeters. This represented the total volume of infarcted myocardium expressed in cubic millimeters. Total infarct volume was expressed as percent of the left ventricle (each normal infarct divided by heart volume, multiplied by a factor of 1.52).[16]

Histologic designates and related phenomena of recently infarcted myocardium were:

Nucleus: pyknosis, deformation, contraction, disintegration and disappearance.

Cytoplasm: loss of striations and fibrillae, coagulation, contraction bands, fragmentation and lysis.

Total fiber: contraction, thinning, waviness, eosinophilia, separation and sequestration (individually and in groups).

Interstitium: edema (with or without muscle fiber edema), inflammatory reaction, hemorrhage, fibroblastosis, angiogenesis and histiocytosis.

Endocardium: edema, hemorrhage, mural thrombi and inflammation.

Epicardium: edema, hemorrhage, inflammation, fibroblastosis, neoangiogenesis and histiocytosis.

Pericardium: fibrin deposits, inflammation, histiocytosis and mesothelial hyperplasia.

Results

Of 57 closed chest dogs that were fully instrumented for intracoronary balloon occlusion or occlusion followed by reperfusion, 17 (30 percent) died during the first 3 hours of occlusion of the proximal left anterior descending coronary artery and were excluded

from further consideration in this study. The 40 dogs that survived the 3 hour occlusion period were randomly divided, 21 in the control group (Group A, 7 days of occlusion) and 19 in the reperfusion (Group B, 3 hours of occlusion followed by 7 days of reperfusion). Of the 21 dogs in Group A, 14 (67 percent) died before the 7th day and 2 surviving dogs were excluded because of supervening bacterial abscess of the myocardium. Thus, complete data were obtained in only five dogs in the control group during 7 days of coronary occlusion. Of the 19 dogs in Group B, 7 (37 percent) died before the 7th day of reperfusion, 2 were excluded because left anterior descending coronary arterial thrombosis occurred and the exact time could not be determined, and 4 others were excluded because of incompleteness of regional metabolic or hemodynamic data due to technical problems or very abnormal control data due to unforeseen illness of the animal. Thus, only six dogs with a complete set of measurements could be validly placed in Group B.

Control Group A: 7 Days of Occlusion (Five Dogs)

This group constituted a control series and underwent procedures identical to those used in Group B except that reperfusion was not performed.

Hemodynamic Measurements (Fig. 1 to 3)

Heart rate: Heart rate before coronary occlusion ranged from 64 to 105 beats/min (averaging 88). Over a period of 3 hours of occlusion average heart rate rose to 105 beats/min. After 7 days of occlusion the heart rate had increased substantially in all five dogs (mean 154 beats/min, a significant rise [$P < 0.002$] relative to the preocclusion level).

Peak systolic pressure: Average systolic pressure before occlusion was 150 mm Hg (range 138 to 168). It decreased 10 percent to 136 mm Hg during 3 hours of coronary occlusion, with little further change (132 mm Hg on the 7th day of occlusion).

Left ventricular end-diastolic pressure: Before occlusion left ventricular end-diastolic pressure ranged from 0.5 to 10 mm Hg (average 4). It increased slightly to 4.5 mm Hg over a period of 3 hours of occlusion and was unchanged on the 7th day.

Maximal left ventricular dP/dt: Mean dP/dt before coronary occlusion was 3,040 mm Hg/sec (range 2,270 to 3,720). A substantial decrease of 37 percent occurred during the first 3 hours of occlusion; however, on the 7th day it was only 7 percent below the preocclusion control level. In four dogs dP/dt returned to normal, but in one dog it was sharply lower (Fig. 2).

Cardiac output: Average cardiac output before coronary occlusion was 3,230 ml/min (range 2,160 to 4,090). A mean 20 percent reduction in cardiac output was observed after 3 hours of occlusion; however, on the 7th day it was only 6 percent below the control level. Substantial restoration of cardiac output was noted in three dogs, whereas the other two dogs exhibited persistent reduction in cardiac output.

Systemic vascular resistance: During 3 hours of coronary occlusion mean systemic vascular resistance rose 23 percent above the control value of 3,170 dynes sec cm^{-5}. However, on the 7th day it returned to the preocclusion control level in all except one dog.

Stroke work: Mean stroke work was 69 g-m/beat during the preocclusion control period and decreased 35 percent during 3 hours of occlusion. Each of the five dogs had a sharply reduced stroke work on the 7th day, largely because of the increase in heart rate.

Coronary sinus blood flow: Mean coronary sinus blood flow was 125 ml/min in the control period (range 106 to 145), decreased 15 percent 3 hours after occlusion and increased to 131 ml/min on the 7th day. In one dog, coronary sinus flow remained depressed (90 ml/min on the 7th day vs. 116 ml/min in the control period).

Ejection fraction: Limited ventriculographic data indicate an average of 0.50 ejection fraction during the preocclusion control period. It decreased to 0.27 at 3 hours of occlusion and then remained depressed at 0.26 on the 7th day of occlusion.

Metabolism (Fig. 1 to 3A)

Myocardial lactate balance ([arteriovenous/arterial] × 100) (percent): *Nonoccluded zone (coronary sinus blood sampling):* During the preocclusion control period, an average 38 percent lactate balance was measured in the coronary nonoccluded region of the left ventricle. Within 5 minutes of the acute occlusion of the left anterior descending artery, mean lactate balance decreased significantly to 15 percent; however, in two dogs, lactate balance remained within normal limits (Fig. 1 and 3A). Average lactate balance at 3 hours of occlusion was 27 percent, and on the 7th day was 24 percent, which represented a persisting significant ($P < 0.05$) reduction in nonoccluded region lactate extraction.

Occluded zone (great coronary vein blood sampling): Mean lactate extraction was 39 percent in the preocclusion control period. At 5 minutes of coronary occlusion, lactate production (−8 percent) was noted in the occluded zone. Deranged lactate balance persisted throughout the 3 hours at −17 percent, and on the 7th day it was −0.6 percent. In two of the five dogs lactate measurements on the 7th day indicated a marked difference between the occluded and nonoccluded zones with lactate production occurring in the occluded zone (Fig. 1 to 3A).

Myocardial potassium balance (arteriovenous) (mEq/liter): *Nonoccluded zone:* In the preocclusion control period, mean potassium balance was −0.01 mEq/liter. Five minutes after coronary occlusion, the nonoccluded zone exhibited a mean potassium balance of −0.15 mEq/liter that continued to 3 hours of occlusion and was 0.06 mEq/liter on the 7th day of occlusion.

Occluded zone: Mean potassium balance was on the average −0.04 mEq/liter in the control period, decreased to −0.34 mEq/liter at 5 minutes of occlu-

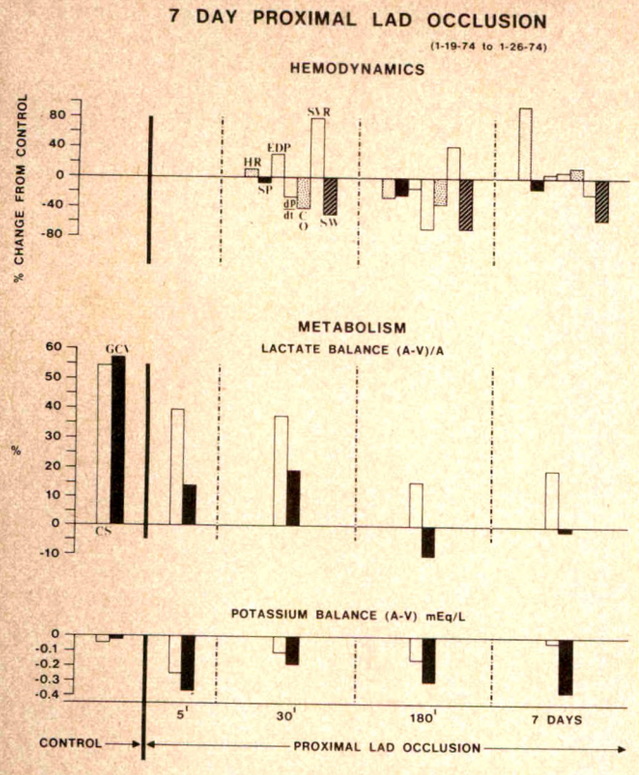


FIGURE 1. Bar graph of data in individual dogs during 7 days of occlusion of the proximal left anterior descending coronary artery (LAD). In the preocclusion period, control hemodynamic measurements were: heart rate (HR) 98 beats/min, systolic pressure (SP) 168 mm Hg, left ventricular end-diastolic pressure (EDP) 9 mm Hg, dP/dt 3,240 mm Hg/sec, cardiac output (CO) 3,350 ml/min, systemic vascular resistance (SVR) 2,930 dynes sec cm^{-5}, stroke work (SW) 75 g-m/beat. Infarct size was 50 percent of the left ventricle. A = arterial; A-V = arteriovenous; CS = coronary sinus; GCV = great cardiac vein.

sion and was −0.28 mEq/liter at 3 hours of occlusion. After 7 days of occlusion potassium balance values had returned to near normal. However, in one of the five dogs (Fig. 1) substantial potassium loss (−0.37 mEq/liter) persisted on the 7th day.

Oxygen extraction (arteriovenous) (percent saturation): The control values in the nonoccluded and occluded region were 66 and 67 percent, respectively, and there were no significant alterations during the 7 days of occlusion.

Histopathology

In Group A, the mean microscopically verified infarct was 31.6 percent of the left ventricular wall volume (individual values: 14, 16, 32, 46 and 50 percent). The primary area of infarction, within the distal half to two thirds of the left ventricular anterior wall, included broad central areas of transmural infarction in all five dogs. Focal subendocardial infarction was noted in the distal posterior left ventricular wall, as well as the adjacent right ventricular wall in all the hearts. In areas of small or focal infarcts within the primary ischemic zone or beyond, the age and characteristics of necrosis and reparative reaction were similar in the major areas of infarction. The latter, however, also contained foci of more recent myocardial infarction and degeneration, suggesting continuing or recrudescing localized ischemia. The anterior wall infarcts were characterized by patchy and confluent coagulative muscle necrosis, sharply marginated by proliferating fibroblasts, and endothelial cells (angiovascular hyperplasia) with variable numbers of inflammatory cells. The preinfarctive marginal zone of proliferating cells extended outwardly between apparently intact, functional-appearing cardi-

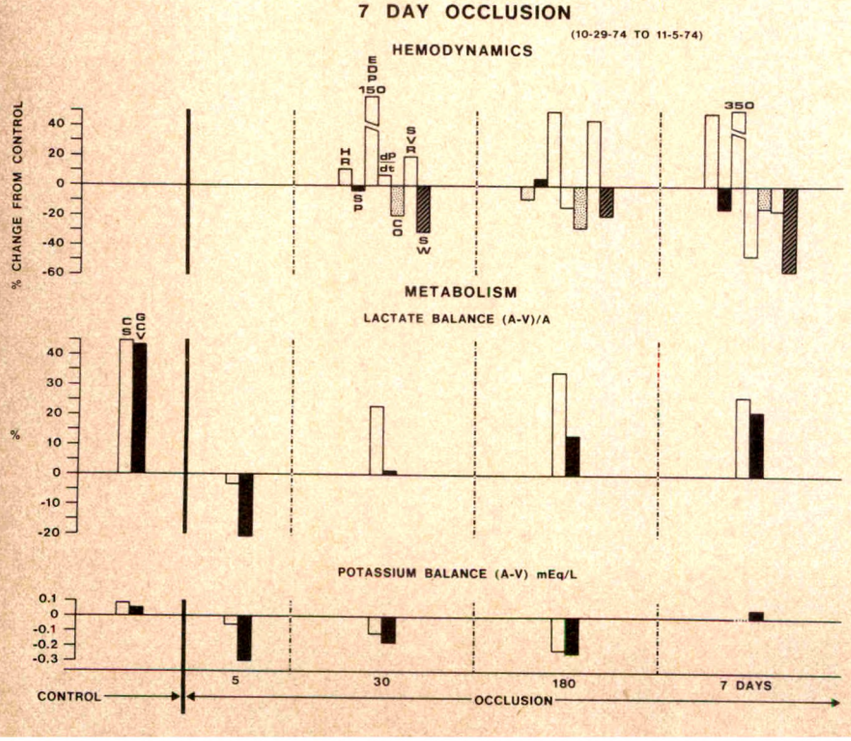


FIGURE 2. Hemodynamic, lactate and potassium data in a dog after 7 days of occlusion of the left anterior descending coronary artery. Control values were: heart rate 105 beats/min, systolic pressure 144 mm Hg, left ventricular end-diastolic pressure 1 mm Hg, dP/dt 3,000 mm Hg/sec, cardiac output 3.67 liters/min, systemic vascular resistance 2,940 dynes sec cm^{-5}, stroke work 70 g-m/beat. Infarct size was 15 percent. Abbreviations as in Figure 1.

ac fibers. However, totally entrapped groups of myocardial fibers appeared to range from normal-appearing through various degrees of degeneration, and acute necrosis (Fig. 4). Fibrinous organizing pericarditis and endocarditis (with mural thrombi) were found in most of the hearts.

Group B: Three Hours of Coronary Occlusion Followed by 7 Days of Reperfusion (Six Dogs)

The preparation of Group B animals was identical to that of Group A except that reperfusion was instituted after 3 hours of coronary occlusion by deflating the intracoronary balloon.

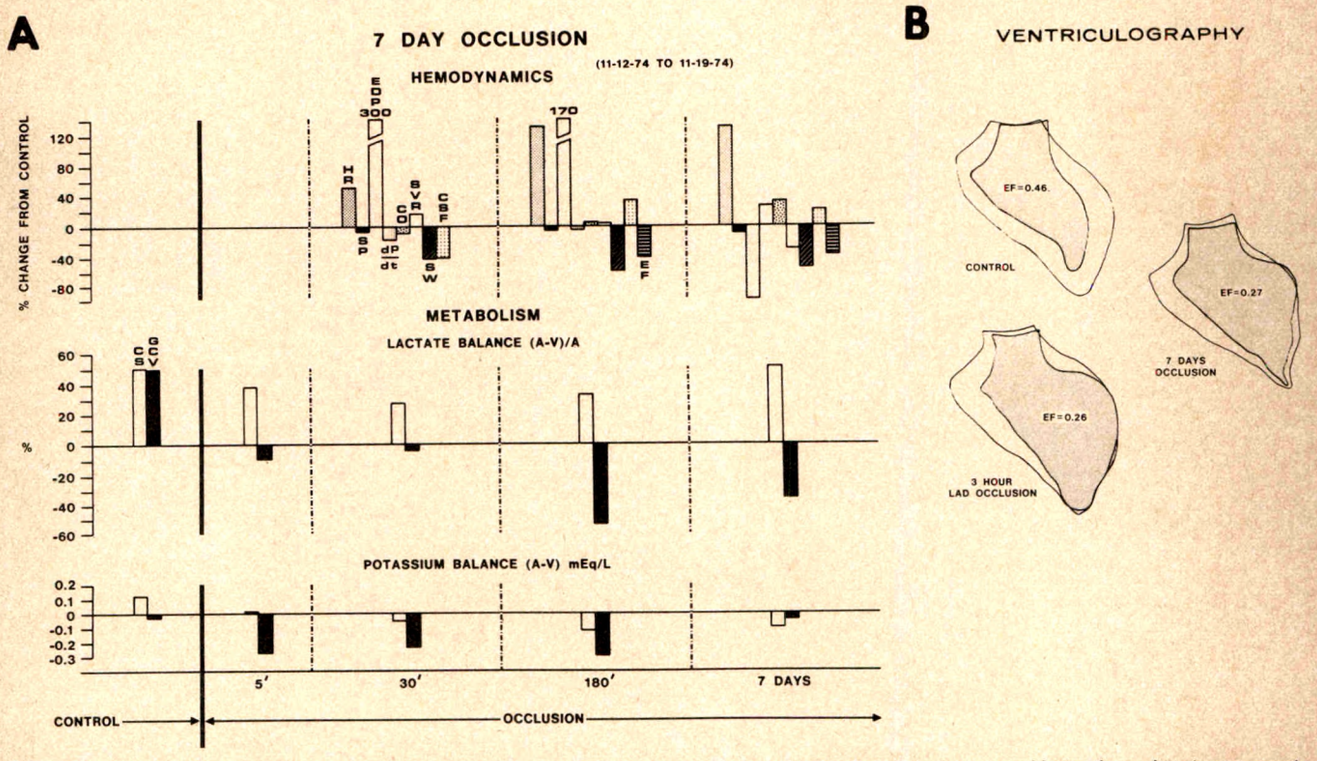


FIGURE 3. A, hemodynamic and metabolic data in a dog after 7 days of coronary occlusion. Preocclusion control hemodynamic measurements were: heart rate 64 beats/min, systolic pressure 138 mm Hg, left ventricular end-diastolic pressure 1 mm Hg, dP/dt 2,270 mm Hg/sec, cardiac output 2.86 liters/min, systemic vascular resistance 3,007 dynes sec cm^{-5}, stroke work 82.8 g-m/beat, coronary sinus flow (CSF) 121 ml/min. **B,** ventriculograms before and after 7 days of persistent occlusion in the same dog. Infarct size was 14 percent of the left ventricle. EF = ejection fraction; other abbreviations as in Figure 1.

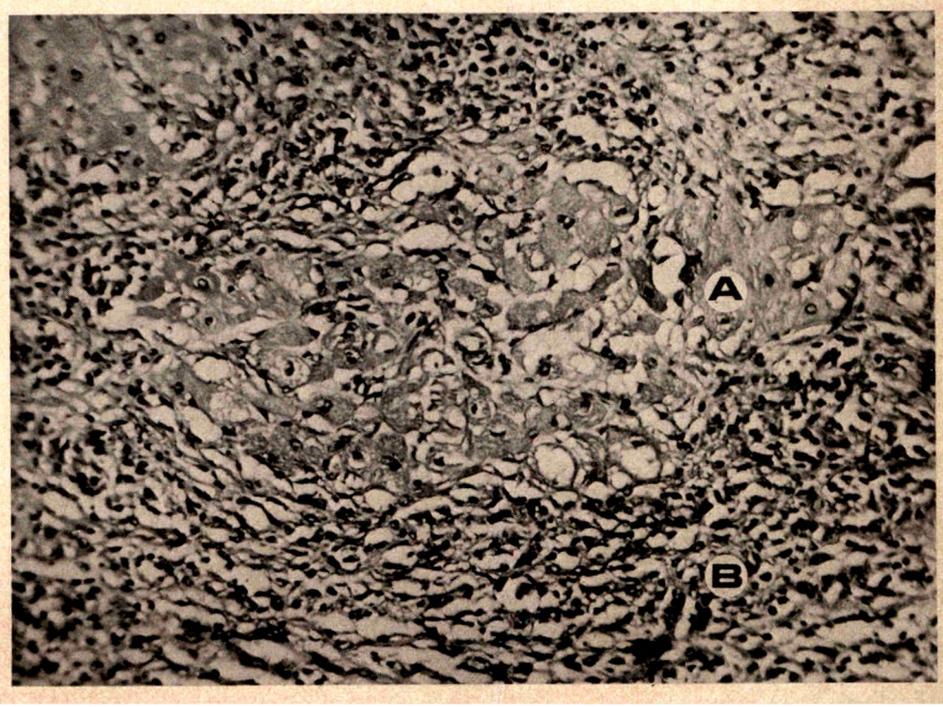


FIGURE 4. Photomicrograph after 7 days of occlusion demonstrating degenerating muscle fibers **(A)** entrapped by granulation tissue **(B).** (Hematoxylin-eosin ×450, reduced by 24 percent.)

Hemodynamics (Table I, Fig. 5 to 10)

Heart rate: In over 3 hours of coronary occlusion the mean heart rate rose 18 percent from a control value of 92 beats/min (range 60 to 120). During the 1st hour of reperfusion, a further increase in heart rate to 24 percent above control level was noted. However, heart rate decreased to 17 percent above control level on the 7th day of reperfusion. Three of the six dogs had a heart rate of more than 15 percent above control value on the 7th day (Fig. 6A and 8A).

Peak systolic pressure: Before coronary occlusion mean peak systolic pressure was 160 mm Hg (range 146 to 189). During the 3 hour period of occlusion mean systolic pressure decreased 8 percent from control level and remained at this level during early and late reperfusion. Individual data indicated that extended reperfusion resulted in a partial return of systolic pressure toward control level in two dogs, whereas in four dogs it was further reduced (5 to 17 percent).

Left ventricular end-diastolic pressure: Mean left ventricular end-diastolic pressure was 8 mm Hg (range 6 to 11) in the preocclusion control period. It increased 33 percent after 3 hours of coronary occlusion. Early during reperfusion (1 hour) there was a further increase to 43 percent above control level. At this time it was above control level in five of the six dogs. On the 7th day mean end-diastolic pressure was 11 mm Hg.

Maximal left ventricular dP/dt: Mean dP/dt was 3,220 mm Hg/sec in the control period (range 1,750 to 4,810). There was a decrease of 36 percent in mean dP/dt during the 3 hour period of occlusion. After 60 minutes of reperfusion it was 48 percent below control level, but in 7 days of reperfusion it returned to within 3 percent of control level. In three of the six dogs, dP/dt remained depressed (11 to 39 percent below control values) throughout the reperfusion period (Fig. 6A, 7A and 9A) and in the remaining three dogs it exhibited a rise.

Cardiac output: Three hours of coronary occlusion caused a 29 percent reduction in mean cardiac output below the control level of 3,060 ml/min (range 2,100 to 3,990). After 1 hour of reperfusion cardiac output

TABLE I

Hemodynamic and Metabolic Data in Six Dogs (mean ± standard error of the mean)

	Control Values	Time After Coronary Occlusion			Time After Coronary Reperfusion		
		5 Min	30 Min	3 Hr	5 Min	1 Hr	7 Day
Heart rate (beats/min)	92 ±10		111 ±13	109 ±12		114 ±12	108 ±10
Peak systolic pressure (mm Hg)	160 ±7		142* ±6	148 ±5		147 ±9	148 ±5
LV end-diastolic pressure (mm Hg)	8 ±0.7		9.6 ±1.0	11 ±1.6		11.8 ±2.2	10.6* ±1.1
Max LV dP/dt (mm Hg/sec)	3220 ±425		2530* ±303	2070 ±267		1670* ±98	3140† ±305
Cardiac output (ml/min)	3060 ±271		2610 ±192	2160 ±312		2570 ±395	3130† ±423
Stroke volume (ml/beat)	34 ±4		26* ±4	20* ±3		23* ±3	31† ±5
Systemic vascular resistance (dynes sec cm^{-5})	3570 ±313		3740 ±402	5140 ±694		4340 ±812	3220 ±445
Stroke work (g-m/beat)	64 ±7.1		40* ±5.0	39* ±5.8		38* ±5.3	48* ±7.1
Coronary sinus flow (ml/min)	132 ±5		55* ±6	97* ±7		119 ±15	136† ±9
Ejection fraction (%)	49 ±5			18* ±1		23* ±1	48† ±4
Lactate balance							
Nonoccluded ([Ao-CS]/Ao × 100)	50 ±2.4	38 ±5.1	38 ±3.2	44 ±4.1	28 ±7.3	37 ±7.1	38 ±3.4
Occluded ([Ao-GCV]Ao × 100)	52 ±2.6	−6.0* ±12.3	0.18* ±8.4	12* ±15.1	8.4* ±4.0	0.8 ±31.0	36 ±5.1
Potassium balance							
Nonoccluded (Ao-CS)	−0.8 ±0.02	−0.27 ±0.06	−0.11 ±0.03	−0.15 ±0.03	−0.13 ±0.06	−0.11 ±0.05	−0.08 ±0.03
Occluded (Ao-GCV)	−0.08 ±0.01	−0.59* ±0.20	−0.32* ±0.06	−0.42 ±0.16	−0.33* ±0.06	−0.34 ±0.11	−0.11 ±0.03

* $P < 0.05$ relative to control value before occlusion.
† $P < 0.05$ relative to value at 3 hours of occlusion.
Ao = aortic; CS = coronary sinus; GCV = great cardiac vein; LV = left ventricular; Max = maximal.

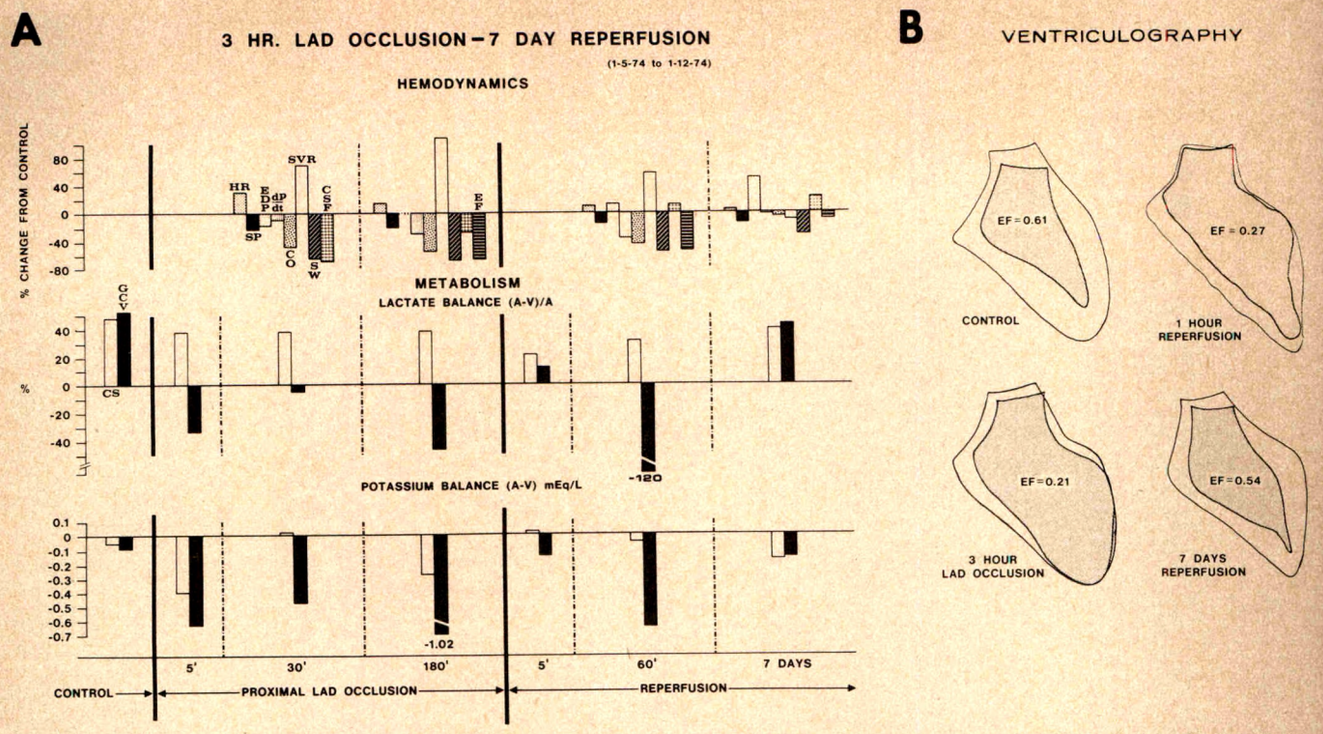


FIGURE 5. A, hemodynamic, lactate and potassium data in a dog after 3 hours of coronary occlusion and 7 days of reperfusion. Control preocclusion hemodynamic measurements: heart rate 120 beats/min, systolic pressure 189 mm Hg, left ventricular end-diastolic pressure 8 mm Hg, dP/dt 3,080 mm Hg/sec, cardiac output 3.46 liters/min, systemic vascular resistance 3,420 dynes sec cm^{-5}, stroke work 67 g-m/beat, coronary sinus flow 132 ml/min, ejection fraction 0.61. **B,** ventriculograms before and after coronary occlusion in the same dog. Marked hypokinesis of the left ventricular anterior wall was noted at 3 hours of occlusion. Infarct size was 9 percent. Abbreviations as in Figures 1 and 3.

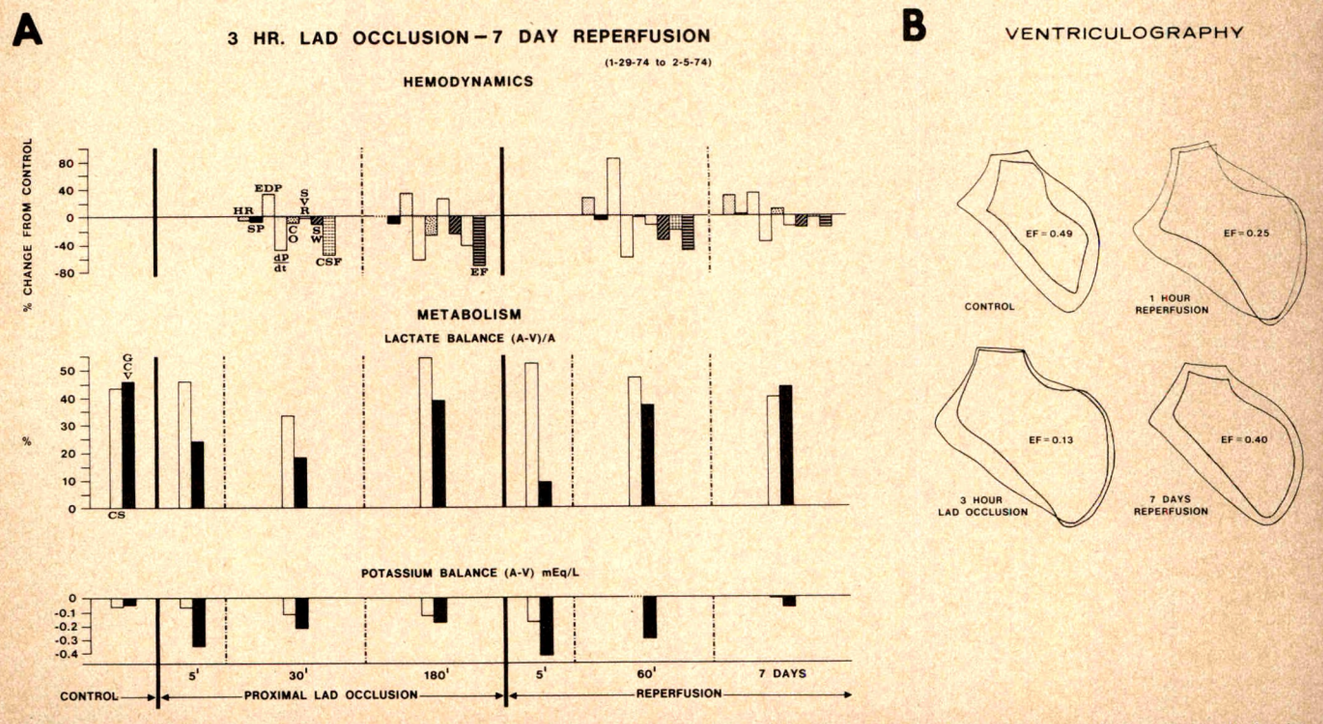


FIGURE 6. A, hemodynamic, lactate and potassium data in a dog with 3 hours of coronary occlusion and 7 days of reperfusion. Preocclusion hemodynamic data were: heart rate 84 beats/min, systolic pressure 148 mm Hg, left ventricular end-diastolic pressure 6 mm Hg, dP/dt 3,940 mm Hg/sec, cardiac output 2.61 liters/min, systemic vascular resistance 3,720 dynes sec cm^{-5}, stroke work 54 g-m/beat, coronary sinus flow 136 ml/min, ejection fraction 0.49. **B,** ventriculograms in the same dog. Infarct size was 23 percent. Abbreviations as in Figures 1 and 3.

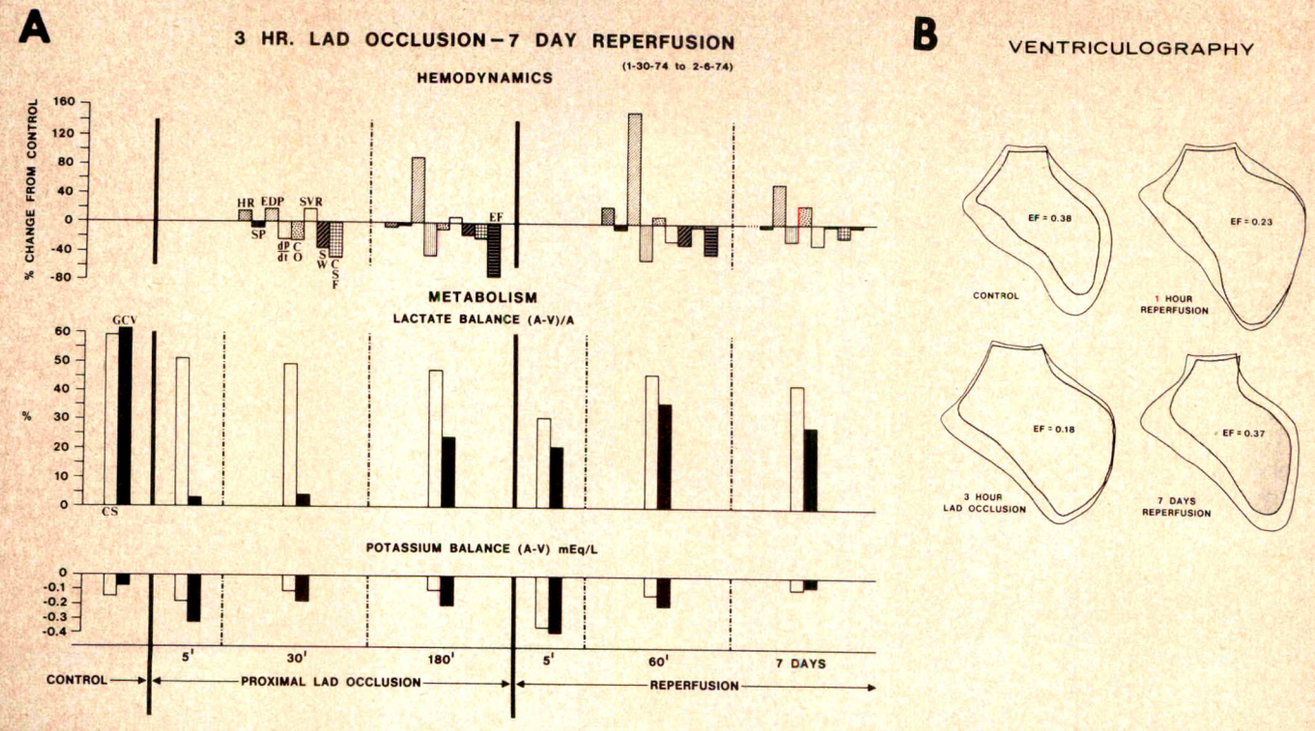


FIGURE 7. A, hemodynamic, lactate and potassium data in a dog with 7 days of reperfusion. Preocclusion hemodynamic measurements were: heart rate 108 beats/min, systolic pressure 164 mm Hg, left ventricular end-diastolic pressure 8 mm Hg, dP/dt 3,650 mm Hg/sec, cardiac output 3.99 liters/min, systemic vascular resistance 2,910 dynes sec cm^{-5}, stroke work 15 g-m/beat, coronary sinus flow 142 ml/min, ejection fraction 0.38. **B,** ventriculograms in the same dog. Measured infarct size was 1.5 percent, indicating dissociation between cardiac mechanical function and extent of infarction. Abbreviations as in Figures 1 and 3.

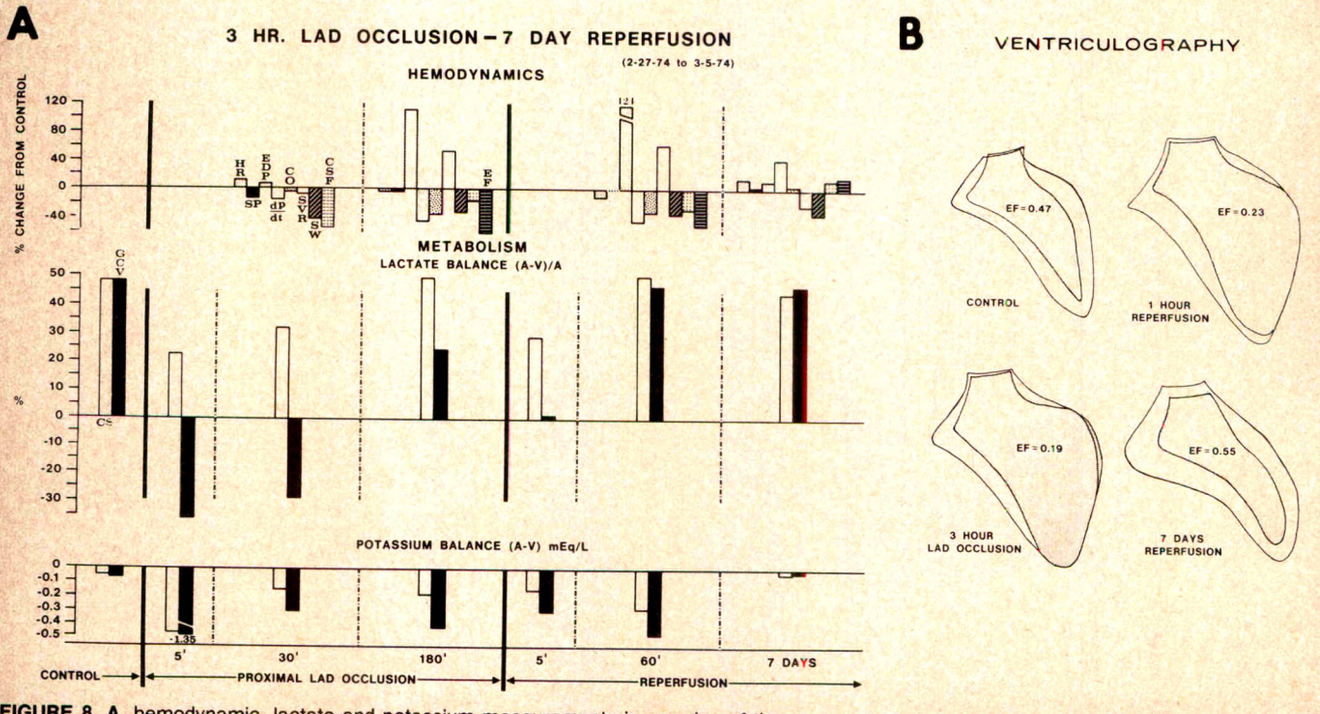


FIGURE 8. A, hemodynamic, lactate and potassium measurements in one dog of the group with 7 days of reperfusion. Hemodynamic control measurements were: heart rate 108 beats/min; systolic pressure 150 mm Hg, left ventricular end-diastolic pressure 8 mm Hg, dP/dt 2,540 mm Hg/sec, cardiac output 2.95 liters/min, systemic vascular resistance 3,420 dynes sec cm^{-5}, stroke work 54 g-m/stroke, coronary sinus flow 117 ml/min, ejection fraction 0.47. **B,** ventriculograms in the same dog. Infarct size was 8 percent. Abbreviations as in Figures 1 and 3.

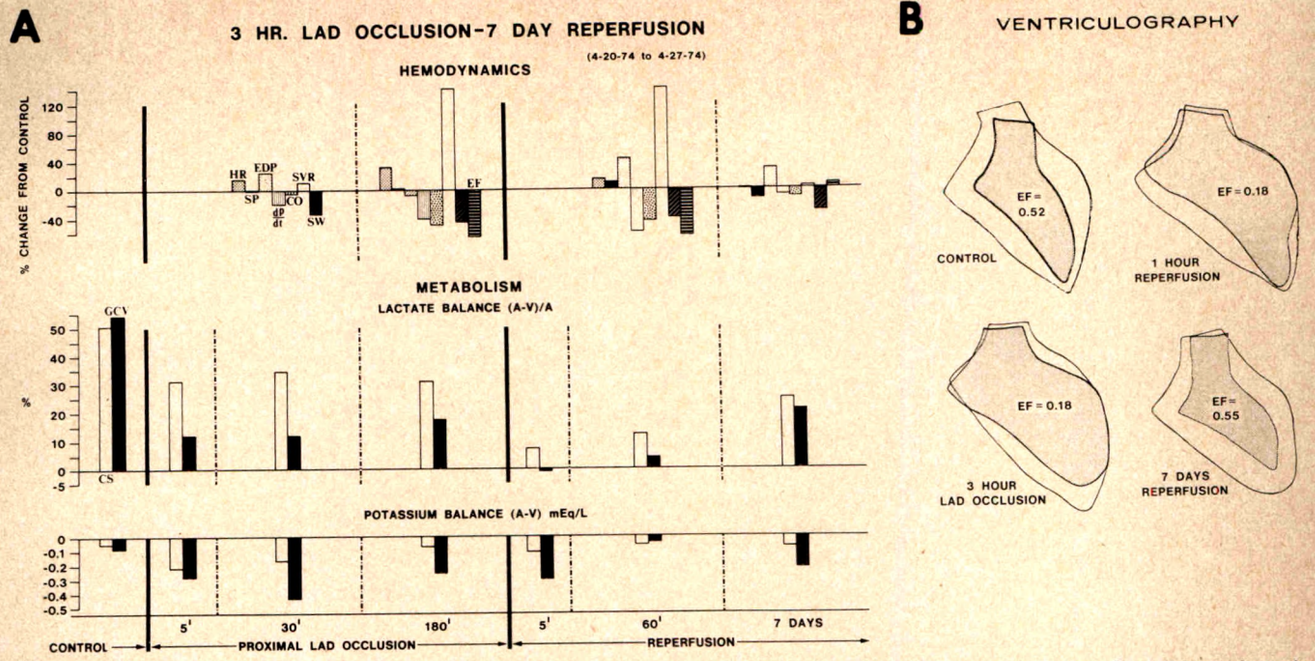
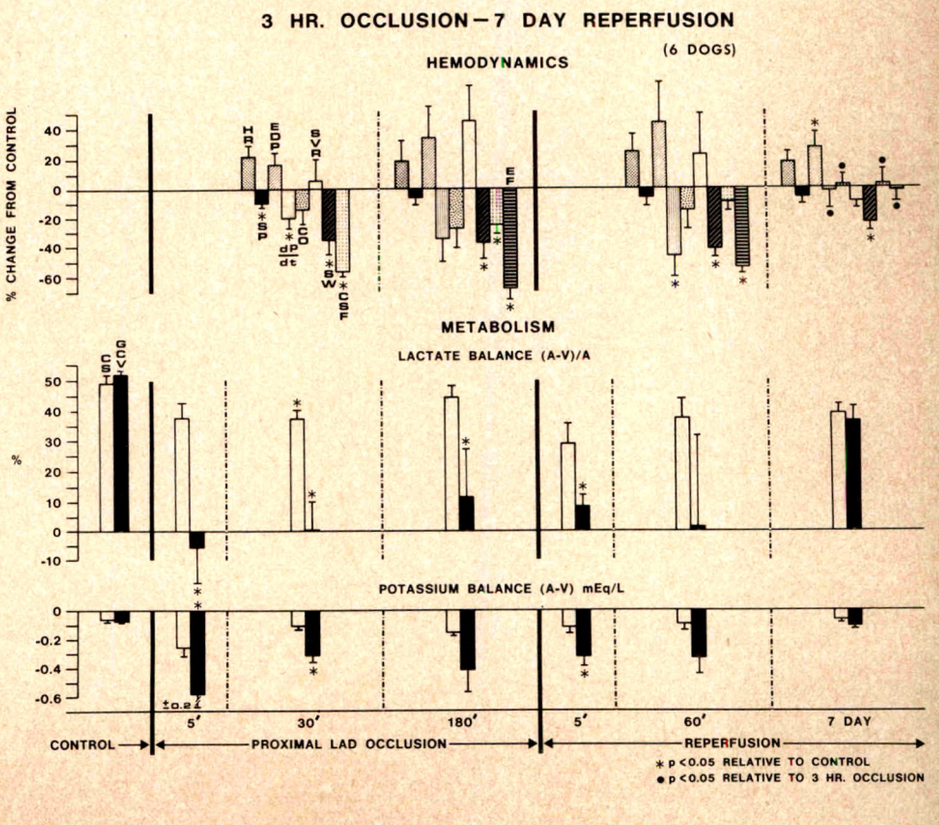


FIGURE 9. A, simultaneous hemodynamic, lactate and potassium measurements in a dog with 7 days of reperfusion. Control hemodynamic measurements were: heart rate 60 beats/min, systolic pressure 164 mm Hg, left ventricular end-diastolic pressure 11 mm Hg, dP/dt 4,810 mm Hg/sec, cardiac output 3.26 liters/min, systemic vascular resistance 2,960 dynes sec cm^{-5}, stroke work 91 g-m/stroke, ejection fraction 0.52. **B,** ventriculographic studies in same dog. Infarct size was 1 percent. Abbreviations as in Figures 1 and 3.

FIGURE 10. Statistical summary (six dogs) of hemodynamic and metabolic measurements during the preocclusion control period and 30 minutes and 3 hours after proximal occlusion of the left anterior descending coronary artery, and 1 hour and 7 days after the start of reperfusion. Mean hemodynamic data are presented as percent changes from the preocclusion control values listed in Table I. During coronary occlusion there was a significant reduction in dP/dt, stroke work, coronary sinus flow and ejection fraction. Heart rate, left ventricular end-diastolic pressure and systemic vascular resistance increased and cardiac output was reduced. During the 1st hour of reperfusion, all hemodynamic measurements remained depressed. On the 7th day of reperfusion all measurements returned to control levels, except for stroke work, which was reduced. In the early stage of coronary occlusion, mean balances in the occluded zone indicated lactate production and a profound net myocardial potassium loss. After reperfusion, lactate and potassium balances at first remained abnormal, but returned to normal levels on the 7th day of reperfusion. Abbreviations as in Figures 1 and 3.



was 16 percent below the control level, and then rose to 2 percent above the preocclusion control level on the 7th day. In three of the six dogs, cardiac output remained 7 to 15 percent below control value after 7 days of reperfusion (Fig. 5A and 9A). In the remaining three dogs 7 days of reperfusion achieved a marked improvement in values relative to those obtained after 3 hours of occlusion and 1 hour of reperfusion (Fig. 6A, 7A, 8A).

Systemic vascular resistance: Mean systemic vascular resistance was 3,570 dynes sec cm^{-5} in the control period, increased 44 percent during the 3 hour occlusion period, and then dropped to 22 percent above control value after 60 minutes of reperfusion and to 10 percent below control value after 7 days of reperfusion. Three hours of occlusion resulted in increased systemic vascular resistance in five of the six dogs, and after 7 days of reperfusion it decreased in five of six animals.

Stroke work: During the control period mean stroke work was 64 g-m/beat. After 3 hours of occlusion it decreased 39 percent. There was little change during the early reperfusion period (41 percent below control value), but it improved slightly to 25 percent below control value at the end of the 7th day. Stroke work during the 1st hour of reperfusion remained below control value in all cases (−28 to −58 percent). Relative to 3 hours of coronary occlusion, 7 days of reperfusion caused an improvement in five of the six dogs (Fig. 5A to 9A).

Coronary sinus blood flow: Mean coronary sinus flow during the control period was 132 ml/min (range 117 to 142). It decreased to 26 percent below control level during 3 hours of occlusion and returned to 3 percent above control level after 7 days of reperfusion. Two of the dogs exhibited a hyperemic response immediately after reperfusion.

Ejection fraction: Mean ejection fraction determined by ventriculography was 0.49 in the control period and dropped to 0.18 after 3 hours of coronary occlusion. It improved only slightly to 0.23 after 1 hour of reperfusion but increased markedly to 0.48 on the 7th day. In all cases, extended reperfusion brought about an improvement in ejection fraction relative to values in the 3 hour occlusion and early reperfusion periods.

Metabolism (Table I and Fig. 3 to 8)

Lactate balance ([arterovenous/arterial] × 100) (percent): Myocardial lactate balances were determined for the occluded and nonoccluded segments of the left ventricle.

Nonoccluded zone: Mean lactate balance in the preocclusion control period was 50 percent, indicating normal extraction. Occlusion resulted in transient derangements, but the mean extraction was 44 percent after 3 hours of occlusion and 37 and 38 percent at 1 hour and at 7 days of reperfusion, respectively. In one dog lactate balance, which was depressed to less than 20 percent after 1 hour of reperfusion, improved in 7 days (Fig. 9A). All six dogs had normal lactate metabolism on the 7th day of reperfusion (range 25 to 45 percent).

Occluded zone: Mean lactate balance in the control period was 52 percent extraction. After 5 minutes of occlusion it was −6 percent, signifying lactate production, and at 3 hours of occlusion there was still deranged lactate balance (12 percent).

Distinct early reperfusion lactate washout was noted in three dogs (Fig. 6A, 8A and 9A). At 1 hour of reperfusion, lactate balance in the previously occluded zone was deranged (0.8 percent), but mean lactate balance returned to 36 percent after 7 days of reperfusion. Three dogs at 1 hour of reperfusion exhibited lactate extraction below 20 percent in the previously ischemic zone (Fig. 5A and 9A). In four of the six dogs derangement in lactate balance was noted shortly after occlusion, but there was improvement at 3 hours of occlusion in two of these four dogs. On the 7th day of reperfusion lactate metabolism in all dogs was returning to normal.

Potassium (arteriovenous) (mEq/liter): Control myocardial potassium balance was −0.08 mEq/liter in both the occluded and nonoccluded regions.

Nonoccluded zone: After 5 minutes of occlusion, this zone exhibited a mean myocardial potassium balance of −0.27 mEq/liter and after 3 hours of occlusion it was −0.15 mEq/liter. Early reperfusion measurements (1 hour) revealed a potassium balance of −0.11 mEq/liter, but the value returned to preocclusion control level on the 7th day.

Occluded zone: Mean potassium balance at 5 minutes of coronary occlusion was −0.59 mEq/liter. After 3 hours potassium balance was −0.42 mEq/liter. Early reperfusion caused a significant potassium "washout" in two animals (Fig. 6A and 7A). After 1 hour of reperfusion, there was a mean potassium balance of −0.34 mEq/liter and on the 7th day potassium balance returned to near control level (−0.11 mEq/liter).

Oxygen extraction (arteriovenous) (percent saturation): During the control period oxygen extraction was 66 percent and 60 percent in the nonoccluded and occluded regions, respectively. Except for reduced oxygen extraction during the earliest period of reperfusion, there were no significant alterations during coronary occlusion or reperfusion.

Histopathology

In Group B, the mean microscopically verified infarct was 14.2 percent of the left ventricular wall volume. Two of the six dog hearts had minute left ventricular wall infarcts of 1 and 1.5 percent of left ventricular volume but two others had infarct volumes of 43 percent and 23 percent, respectively. The remaining two dog hearts had intermediate-sized infarcts of 8 and 9 percent, respectively. The primary area of infarction, within the distal half to two thirds of the left ventricular anterior wall, included small central zones of transmural infarction, only when the infarct size was greater than 5 percent of the left ventricular volume.

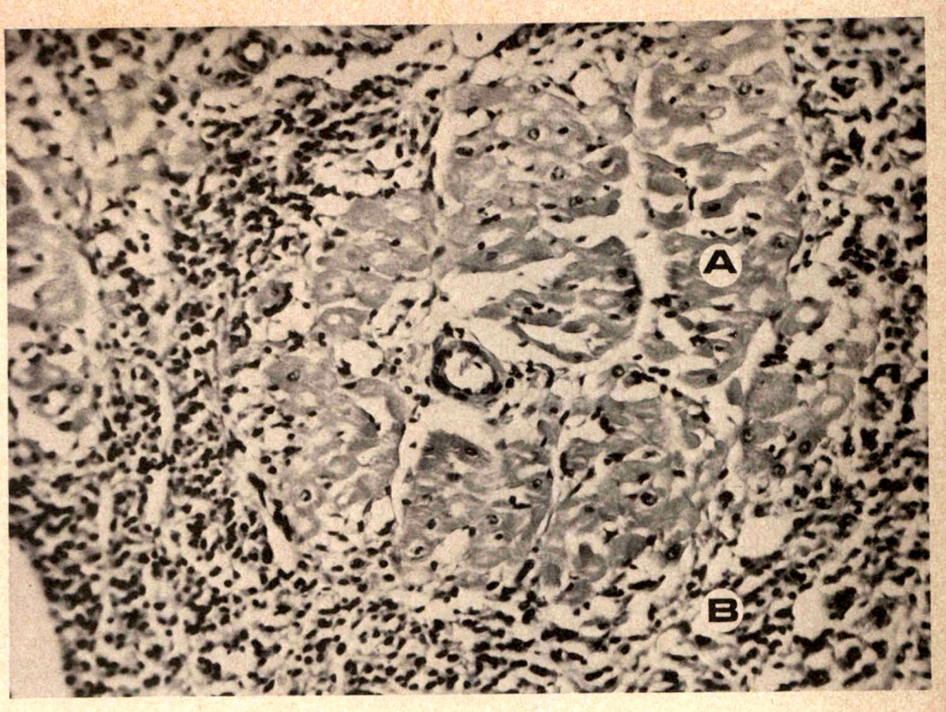


FIGURE 11. Demonstration of myocardium entrapped by granulation tissue **(B)** exhibiting intact muscle fibers **(A)** after 3 hours of occlusion and 7 days of reperfusion. Note the vessel in the middle of the island of salvaged myocardium. (Hematoxylin-eosin ×450, reduced by 24 percent.)

Recent hemorrhages characterized the infarcts in all of these dog hearts. The marginal zones of reparative fibroblastosis and neoangiogenesis about all infarction sites were broader and larger than in the control group. A prominent relation of these reparative zones centered around venous channels (Fig. 11). There were fewer and smaller foci of various stages of myocardial infarction and degeneration involving granulation tissue and entrapped myocardial fibers peripheral to the zone of major organizing infarction than in the control group. In all hearts of this series (Group B), the borders of infarction were far less demarcated than in Group A. The fibrinous organizing pericarditis and endocarditis (with mural thrombi) were lesser in degree and frequency than in the control group.

Discussion

Although many lives have been saved in the past decade as a result of new concepts in the aggressive management of cardiac infarction, including use of electrocardiographic monitoring techniques and early application of electrical countershock by specially trained coronary care personnel, management of acute infarction continues to present a significant challenge to the cardiologist, cardiac surgeon and basic investigator. More recently, physiologic monitoring has been developed, which provides a control of specific pharmacologic and mechanical manipulations to optimize preload and afterload of the failing ventricle.

Factors and Interventions Affecting Infarct Size

Considerable interest is now being focused on recent research data suggesting that infarct size might be minimized by certain pharmacologic or mechanical interventions.[16,17] Revascularization after acute coronary occlusion has been advocated because it might significantly improve cardiac function, minimize the eventual infarct size and increase survival.[18] Among the basic questions requiring early resolution is how long after an acute coronary occlusion myocardial tissue will remain viable to permit effective interventions, and also what are the potential benefits or hazards of revascularization.

It was previously believed that the fate of the ischemic myocardium was determined at the time of an acute coronary occlusion. Some investigators lead us to assume that 60 minutes after an occlusion most of the ischemic myocardium becomes irreversibly damaged so that subsequent intervention would not influence the infarct.[6] This concept is largely derived from pioneering studies in open chest dogs in which acute occlusion of the left circumflex coronary artery was followed by extensive histopathologic analysis of the left ventricular posterior papillary muscle. Because this muscle lacks the collateral blood supply exhibited by other segments of the left ventricle, caution must be used in applying these data to regions of the heart that have collateral circulation and thus might withstand longer periods of acute occlusion. The problem of saving regionally ischemic and jeopardized myocardium is now being restudied for various sites of coronary occlusion.[19,20] In addition, evidence and concepts of remote myocardial metabolic infarction cause us to believe that all parts of the heart may have to be considered jeopardized after an acute coronary occlusion.[21–25]

Several reports[11,20] have indicated that acute cardiac infarction might be controlled and infarct size

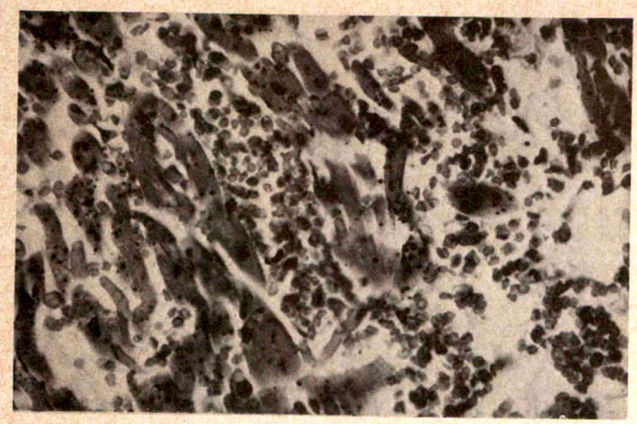


FIGURE 12. Muscle fiber degeneration observed after 3 hours of occlusion followed by 30 minutes of reperfusion. Note the early reperfusion derangements including intracellular and extracellular edema and extravasated red blood cells. (Hematoxylin-eosin ×450, reduced by 28 percent.)

reduced by manipulations applied as long as 3 to 5 hours after occlusion of the proximal left anterior descending artery. Among interventions being considered[16] are: (1) increasing myocardial oxygen supply through oxygen administration, enhanced oxygen diffusion, coronary vasodilatation, revascularization or coronary venous retroperfusion; (2) reduction of oxygen demands by optimizing left ventricular afterload and preload; (3) enhancement of cell membrane transport; (4) reduction of intracellular swelling and interstitial edema to promote reflow of blood; and (5) improvement of autolytic processes. It is difficult to assess the influences of any of these interventions on the coronary-occluded myocardium, chiefly because there are as yet no reliable methods of measuring the regional dynamics of progressive infarction or quantitating infarct size in the beating heart. Evaluation of benefits or drawbacks of treatment requires comprehensive determinations of regional metabolic, mechanical and electrophysiologic function and hemodynamic status of the cardiac and systemic circulations.

Our study focused specifically on the question whether ischemic myocardial damage can be modified by restoring coronary arterial blood flow after 3 hours of occlusion of the proximal left anterior descending coronary artery. Previous investigations performed in a closed chest intracoronary balloon occlusion-reperfusion model revealed that 5 hours of reperfusion after 3 hours of such occlusion failed to improve and often caused further deterioration in hemodynamic indexes as well as myocardial metabolism.[12] Our current objective was to establish in the same preparation whether such derangements persist during a more prolonged period of revascularization. Simultaneous regional myocardial metabolic, mechanical and hemodynamic measurements were obtained in this study after a 3 hour period of occlusion and after reperfusion lasting 7 days. These data and measurements of infarct size were contrasted with findings in a control series with 7 days of constant occlusion. Because of the high mortality rate associated with coronary occlusion or reperfusion of the proximal left anterior descending coronary artery and certain technical difficulties, the size of the series is limited. We attempted to duplicate the site of occlusion in the left anterior descending coronary artery in each dog by placing the intracoronary balloon immediately distal to the first diagonal branch of this artery and estimated that approximately 30 to 40 percent of the left ventricle was rendered ischemic by the acute occlusion produced in our preparation. However, inevitable variations in coronary vasculature and particularly in the degree of overlapping and collateral circulations preclude achievement of identical areas of ischemia.

Pathologic Studies—Effects of Occlusion, Consequences of Reperfusion

The most striking difference between the control group (Group A, 7 days of occlusion) and Group B (3 hours of occlusion, 7 days of reperfusion) was in the resulting infarct size. In the control group, mean infarct size was 31.6 percent of the left ventricular wall volume with three large infarcts of 50, 46 and 32 percent and two lesser infarcts of 16 and 14 percent, respectively. The purpose of the 7 days of reperfusion after the 3 hour period of occlusion was to salvage a substantial portion of the ischemic myocardium from necrotizing infarction. The six surviving dogs had a mean infarct size of 14.2 percent of the left ventricular wall volume, which was about half that of the control group. However, of these six dogs, two had large infarcts of 43 and 23 percent, respectively, two had very small infarcts (less than 1.5 percent) and the remaining two had infarcts of intermediate size (8 and 9 percent, respectively). The variable infarct size encountered in both groups might be attributed to anatomic differences in coronary arterial overlapping or collateral circulation and inadequacies in reflow caused by tissue edema, extravasation of blood cells and cell swelling[26] (Fig. 12). However, in spite of this variability the reduction in infarct size appears to be of clinical significance, suggesting that revascularization might favorably influence the ischemic process and save myocardial tissue.

The determination of infarct size was based upon detailed microscopic analysis. Some investigators have used other methods or reported results of naked eye inspection as to the distribution and degree of infarction. Our experience indicated that naked eye estimates of infarction size were grossly inaccurate, particularly in the presence of hemorrhages, and, on the average, exceeded microscopic evaluation by 45 percent.

Striking differences were noted in the character of the infarcted muscle border zones of the two groups of dogs. In Group A, the ischemic zone of the left ventricular wall had a large central area of infarcted muscle with marginal zones of granulation tissue entrapping clusters of muscle cells. Some of the clusters

showed a progressive range from mild degeneration to irreversible coagulative necrosis, which appeared more recent than that of the major infarction. In contrast, in Group B after 7 days of reperfusion, the corresponding major area of infarcted muscle within the anterior wall of the left ventricle not only was smaller but also included a broader zone of granulation tissue with fewer clusters of entrapped muscle. These clusters appeared more uniformly normal in that degenerative and newly coagulative necrosis was less evident. It appeared, therefore that jeopardized myocardium bordering on zones of major infarction was salvaged through effective reperfusion by way of functioning coronary vessels (Fig. 11).

Another difference between the two groups was the prominent extensive interstitial acute hemorrhage in the area of infarcted muscle, as well as in the adjacent surviving muscle in all dogs subjected to reperfusion (Group B). Similar acute interstitial hemorrhages were found in only one of the hearts of the control group. The source of acute hemorrhage may be periinfarction neoangiogenesis and necrosis of coronary arteries of small to intermediate caliber. Degenerative changes after reperfusion in arteries of small caliber have been previously described.[7,27]

Some investigators[20] have recently concluded that, after 3 hours of occlusion of the proximal left anterior descending coronary artery in the dog, reperfusion would salvage most of the ischemic myocardium, whereas others[7,28] have noted substantial failure of reperfusion to reduce infarct size and have pointed to gross evidence of hemorrhages. Such divergent results might be accounted for by differences in methodology of measurement of infarct size coupled with differences in open chest preparations and in degree of ischemia.

Studies by Whalen et al.[29] on the morphologic features and ion content of canine myocardial cells with ischemia and reperfusion support the hypothesis that loss of cell volume regulation may be one of the primary consequences of myocardial ischemia. Intracellular and interstitial swelling after coronary occlusion is aggravated during the initial phase of revascularization and is believed to cause a "no reflow" state that interferes with reestablishment of perfusion of the myocardium in the early phase of reperfusion, limits nutrition of the ischemic zone and often results in further deterioration of cardiac metabolic and mechanical function. Inadequate reflow may be associated with other functional abnormalities such as deranged membrane permeability and the regulation of cellular ion transport.[26]

In our studies of 30 minutes of reperfusion after 3 hours of coronary occlusion, swelling was one of the earliest recognizable morphologic changes (Fig. 12). A series of chronic experiments revealed that the swelling gradually decreased until it became imperceptible with 4 days of reperfusion after 3 hours of occlusion. It appears that, with extended reperfusion, swelling recedes, reflow is generally reestablished, and mechanical and metabolic function of the left ventricle is restored.

Effects of Occlusion on Cardiac Function

After 3 hours of occlusion of the proximal left anterior descending coronary artery, all dogs sustained regional akinesia or dyskinesia and a considerable decrease in left ventricular ejection fraction. Compromised contractile function was also reflected in measurements of left ventricular stroke volume, maximal dP/dt, stroke work and cardiac output. Abnormal lactate and potassium balance resulted in the region with coronary occlusion, and occasionally pronounced metabolic derangements also occurred in the nonoccluded zone. Oxygen extraction changed minimally.

On the 7th day of occlusion, measurements generally indicated persisting mechanical and metabolic dysfunction. Lactate balance in the occluded zone was abnormal or at production level, whereas potassium balance tended to return to control level. Lactate derangements were also noted in the nonoccluded zone; correlations of this metabolic dysfunction with focal remote infarcts are dealt with in a separate paper.[24] The heart rate on the 7th day of occlusion was invariably increased and ejection fraction as well as stroke volume remained depressed. The persistent severely reduced lactate extraction or production probably reflects the effects of tachycardia on clusters of degenerating but still viable cells in the occluded zone.

Effects of Reperfusion on Cardiac Function

Reperfusion after 3 hours of occlusion did not lead to immediate restoration of contractile metabolic and hemodynamic function. In fact, after 1 hour of revascularization all dogs exhibited persisting pronounced contractile, metabolic and hemodynamic dysfunction relative to the occlusive state immediately before reperfusion. Regional dyskinesia appeared unaltered and left ventricular ejection fraction as well as cardiac stroke volume failed to increase in early reperfusion (Fig. 5 to 9). Maximal dP/dt usually decreased further even though coronary sinus blood flow returned to normal in three of five dogs. Systemic vascular resistance decreased significantly, and cardiac output generally rose above control level at 3 hours of occlusion. Equally striking was the persistence in lactate and potassium derangements at 1 hour of reperfusion. Mean lactate balance in the occluded region, which was 12 percent at 3 hours of occlusion, dropped below 1 percent within 1 hour of initiating reperfusion. Less striking metabolic changes were also noted in the nonoccluded segment. Our data clearly indicate a failure of early reperfusion to reverse dysfunction and confirm trends we have previously reported[12] during the first 5 hours of reperfusion. These experimental observations have profound clinical implications in that revascularization must not be assumed to provide an immediate reversal of left

ventricular dysfunction. We believe that the early hours after bypass surgery in acute infarction constitute a hazardous transition period during which the closest monitoring and suitable treatment may be indicated to prevent serious arrhythmias and development of cardiogenic shock.

Our data on the 7th day of reperfusion are in sharp contrast to those of the early reperfusion period. After 7 days of reperfusion, the surviving dogs exhibited a much improved cardiac function; lactate metabolism returned to near control level, and ventriculograms generally revealed resumed kinesis of the previously dyskinetic or akinetic anterior wall segment. Cardiac stroke volume as well as other hemodynamic measurements corroborated the benefits of prolonged reperfusion. In spite of the early metabolic and mechanical instabilities and potential hazards of dysrhythmias, a period of 7 days of reperfusion was generally found to improve function and enhance survival as compared with 7 days of occlusion. By contrast, the derangements of cardiac function and unsettled morphologic features on the margin of the infarct observed on the 7th day of occlusion, coupled with the finding of a larger mean infarct size and greater mortality in the control series, tend to emphasize the risks involved in not revascularizing in the presence of a major acute coronary occlusion.

Correlation of Infarct Size with Cardiac Function

It appeared from our data that ejection fraction, regional dyskinesia and indexes of contractile function were not related only to the size of the infarct. In the two dogs in Group B with the smallest infarcts (less than 1.5 percent of the left ventricular wall volume), there was apparently good correlation with ejection fraction since the latter returned to control level on the 7th day. However, ejection fraction was also normal in the dog in this group with the largest infarct (43 percent of left ventricular wall volume). There also appeared to be no direct correlation between regional metabolic function and infarct size. In one dog with a large infarct after 7 days of reperfusion lactate extraction returned to normal within 1 hour of reperfusion. By contrast, a similarly large infarct in a dog after 7 days of occlusion was associated with severely deranged metabolism.

Clinical Application of Early Reperfusion After Coronary Occlusion

Surgical revascularization of an acute cardiac infarct has been proposed with a view to reducing infarct size and decreasing mortality in man. This study establishes that reperfusion in dogs significantly decreases mean infarct size, suggesting that the jeopardized myocardium might still be salvageable after longer periods of coronary occlusion than previously deemed possible. However, infarct size was not reduced in some of the hearts, which suggests that 3 hours of coronary occlusion might be approaching the maximal time beyond which ischemic alterations might no longer be reversed. Further investigation is needed to determine whether reperfusion after longer periods of occlusion might be beneficial.

Our reperfusion data differ from those of other investigators who reported failure of reperfusion after shorter periods of coronary occlusion.[30] These differences might be due to specific differences in open chest as compared with closed chest preparations and variations in mode of performing coronary occlusion. The reliability of many different end points used to judge the predicted infarct size, such as alterations in epicardial electrocardiogram or serum creatine phosphokinase levels has recently been questioned. We believe that our method, which provides simultaneous measurements of regional metabolic and mechanical function of both ischemic and nonischemic segments in a closed chest intracoronary balloon occlusion-reperfusion model, provides more meaningful end points than those of previous studies. These measurements, when coupled with detailed pathologic evaluation of infarct size, provide a comprehensive experimental data basis for assessing the effects of revascularization during an evolving myocardial infarction.

A few reports[1–5] indicate that the operative mortality rate of coronary arterial bypass surgery after acute infarction ranges from 14 to 39 percent. Such a wide difference is not surprising because of the wide spectrum of patient population studied, including cases of impending rather than established acute coronary occlusion, and the various intervals between the onset of acute occlusion and the attempt at revascularization. Such operative mortality figures should be contrasted with the average 15 percent mortality rate reported in patients with acute infarction receiving medical treatment in well equipped coronary care units.

In the current study 37 percent of the reperfused group and 67 percent of the control group were excluded because they did not survive the 7 day experimental period. The high mortality rate found in both groups was presumably related to absence of therapy or special care during the 7 day period in the vivarium. Death in the control group occurred throughout the 7 day period. By contrast, death in the reperfused group occurred largely within the early period of reperfusion when hemodynamic, myocardial metabolism and mechanical function remained severely compromised and ominous arrhythmias supervened.

One major finding of our study relates to the unstable period during the early phase of reperfusion. Sequential biopsy studies indicated that the instability of this period is associated with swelling of the ischemic zone. This could result in poor reflow, as shown by other studies demonstrating delayed return of glycogen, phosphorylase and adenosine triphosphatase activity in the myocardium for the first 2 hours of reperfusion.[31]

Severe cardiac dysfunction and arrhythmias are also encountered in man during the early stages of coronary bypass surgery after acute infarction.[12] Our

studies raise the question whether surgical intervention constitutes further jeopardy to the already unstable condition of the patient with acute infarction. Maximal hemodynamic and arrhythmic monitoring and appropriate treatment must be provided during this unstable period. Administration of mannitol and other hyperosmolar agents and corticosteroids that counteract swelling of the myocardium could facilitate "reflow" into the edematous ischemic zone and might salvage some of the jeopardized myocardium.[32] Combined use of counterpulsation and nitroprusside and other pharmacologic agents might also benefit the jeopardized myocardium in the early stage after emergency coronary bypass surgery by reducing cardiac work load and oxygen demands.

Because of these considerations, we must question under what circumstances bypass surgery should be performed after acute infarction. In the early stage of infarction, it might reduce infarct size, but this appears unpredictable and the surgical intervention is associated with significant operative mortality. If the clinical signs and electrocardiogram reveal a massive area of acute myocardial injury, thus suggesting a high risk patient, early revascularization, within 3 hours of occlusion, might be indicated for reduction of infarct size and improvement of function. Such application of emergency bypass procedures necessitates ready availability of cardiac catheterization and surgical teams for performance of angiography and bypass surgery.

This study excluded several animals in which shock developed. The data on these animals will be incorporated in a forthcoming report on cardiogenic shock and reperfusion. The value of revascularization in the treatment of cardiogenic shock remains in question. In 75 percent of patients the onset of the shock state does not become clinically evident until 24 hours after acute infarction and after more than 40 percent of the left ventricle is infarcted.[33] Revascularization in such patients would appear futile since too much time has elapsed to expect reversal of the ischemic damage. However, total circulatory assistance used in performing the coronary bypass procedures might correct the dysfunction of noninfarcted tissue. Because the cardiogenic shock state is accompanied by mortality rates of 80 to 95 percent, further studies are needed to determine whether coronary bypass surgery combined with circulatory assistance and afterload-reducing agents might salvage some of these patients.

We conclude that there are two beneficial effects of revascularization after 3 hours of occlusion: (1) Average infarct size is significantly reduced by prolonged reperfusion after 3 hours of occlusion, although it may be unchanged in individual cases, and (2) restoration of cardiac function usually occurs by the 7th day.

Adverse effects of reperfusion include swelling of the ischemic myocardium caused by interstitial edema, cell degeneration and hemorrhages. Cardiac metabolic and mechanical function remains abnormal or deteriorates further for at least 1 hour after reperfusion. The unstable stage probably results from poor reflow.

Acknowledgment

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Consequences of Coronary Arterial Occlusion on Remote Myocardium: Effects of Occlusion and Reperfusion

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Focal necrosis (microinfarcts) and regional lactate derangements were observed in closed chest dogs in the nonoccluded (remote) posterior segments of the left and right ventricles after acute occlusion of the proximal left anterior descending coronary artery.

Focal infarcts in the remote areas were observed in five of six dogs with 7 days of occlusion of the left anterior descending artery and in six of seven dogs with 7 days of reperfusion after 3 hours of occlusion. There was a good correlation between the finding of microinfarcts and myocardial lactate derangements in the corresponding remote myocardium. No significant lactate derangements or microinfarcts were found in sham experiments. These findings suggest that ischemia of the remote myocardium frequently accompanies an acute coronary occlusion and may result in irreversible focal lesions.

Management of acute myocardial ischemia is usually aimed at treating metabolic and mechanical dysfunction of the coronary-occluded region of the heart. It is normally assumed that the function and morphologic features of the heart remote from the occluded region will remain unimpaired and contribute compensatory hypercontraction to maintain an adequate output. However, newly derived data support the concept that a major coronary arterial occlusion is associated with significant metabolic derangements in both coronary-occluded and nonoccluded zones of the heart.[1–7] We[5] previously reported microinfarcts in the nonoccluded zone after acute coronary occlusion and reperfusion in three dogs, but all had significant hypotension. The question remained unanswered whether such infarcts were due to remote effects of occlusion or reperfusion derangements as such, reduced coronary flow secondary to acute hypotension, or other mechanisms.

This investigation compares regional metabolic measurements in the nonoccluded zone with the subsequent finding of infarcts in the corresponding "remote" area. These closed chest dogs remained normotensive after they were subjected to 7 days of coronary arterial occlusion or 3 hours of occlusion followed by 7 days of reperfusion. Other studies were designed to determine the effects of coronary occlusion upon glycogen content in the remote myocardium.

Methods

Closed Chest Preparation

Simultaneous regional metabolic measurements in both the nonoccluded and occluded myocardial zones after occlusion of the left anterior descending coronary artery were performed during brief separation of coronary venous compartments in the closed chest intracoronary balloon occlusion-reperfusion canine model previously described by us.[5–7] Thus, myocardial lactate and potassium balances were obtained from myocardial zones perfused by either the left anterior descending or left circumflex coronary arteries. The

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methods and procedures as well as specific measurements have been defined previously.[8] The closed chest dog series were: group A, 7 days of continuous occlusion; group B, 3 hours of occlusion followed by 7 days of reperfusion; and group C, fully instrumented sham experiments without coronary occlusion that were observed for 7 days.

The following common pathologic procedure was applied in analyzing the hearts from these series.

Gross and microscopic methods employed in quantitating the size of the anterior left ventricular infarct is presented elsewhere in this Symposium.[8] Since infarcts cannot always be discerned by the naked eye light microscopy is necessary (Fig. 1 to 3). In this study, the "remote area" of myocardium, whose circulation is presumed unaltered by the occluded left anterior descending artery, was divided into three parts: (1) posterior left ventricle, (2) posterior interventricular septum, and (3) right ventricle (lateral and posterior aspects). Each part was independently evaluated by two investigators. Figure 4 shows a typical infarct analysis in myocardial slabs (Dog no. 421).

The myocardial infarction in the remote area presented on the 7th day of occlusion or reperfusion in identical fashion as minute foci of proliferating fibroblasts and endothelial cells and occasional necrotic muscle fibers. Rarely, small confluent foci of coagulated muscle were encircled by variable degrees of proliferating fibroblasts and endothelial

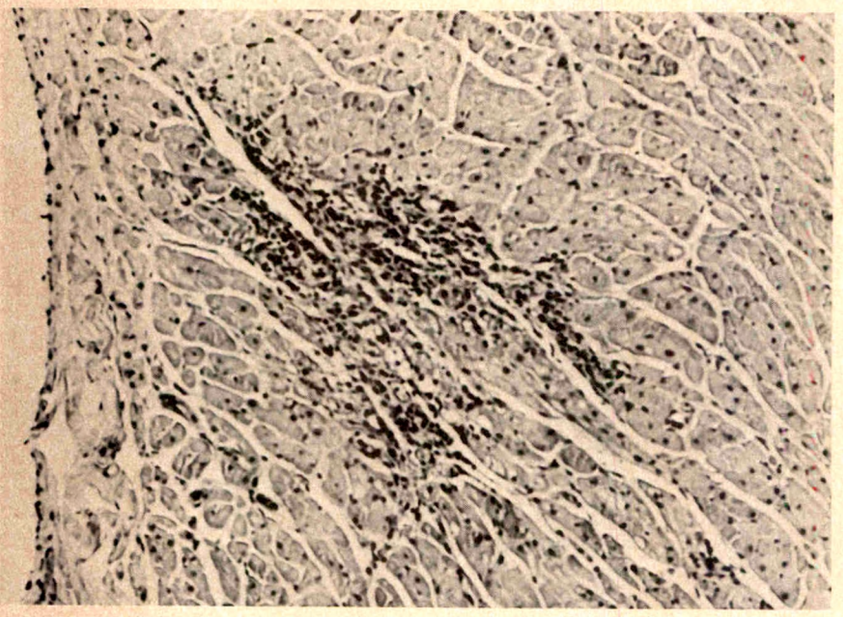


FIGURE 1. Photomicrograph of left ventricular posterior wall showing a remote subendocardial focal infarct in a dog after 3 hours of occlusion and 7 days of reperfusion. Note the demarcated cellular proliferation and infiltration by lymphocytes (hematoxylin-eosin ×500, reduced by 32 percent).

FIGURE 2. Photomicrograph of a "remote area" early focal myocardial infarct 3 hours after occlusion of the left anterior descending coronary artery in sequential zones A through G (biopsy specimen from a dog in another series). The slide exhibits muscle fiber edema in zone A; amorphous myofibrillar granular coagulation with pyknotic nucleus in zone B; confluent coagulative myoplasm necrosis in zone C; disintegration by lysis of necrotic muscle fiber with nuclear change resembling histiocytosis in zone D; myocytolysis with empty shells of muscle fibers containing vacuolated muscle-histiocytes, pyknotic sarcolemmal nuclei in zone E; capillary channel with increased number of endothelial cells in zone F; myocytolysis with vacuoles, vague shadows of residual cross striation, intrafiber lymphocytes in zone G (hematoxylin-eosin-eosin ×800, reduced by 31 percent).

cells. Such infarcts, on this 7th day of host response, were measured as volume in cubic millimeters. Any observed arterial or venous occlusion, (in addition to the left anterior descending artery occlusion) were identified.

The closed chest intracoronary balloon occlusion-reperfusion model features regional measurement of myocardial metabolism. Metabolic data from the nonoccluded left ventricular posterior zone were obtained by simultaneous blood sampling from the aorta and coronary sinus in the presence of brief temporary balloon occlusion of the great cardiac vein. Thus, sampled coronary venous blood essentially represented drainage of the left circumflex coronary system. Lactate extraction or production in the nonoccluded zone, measured during occlusion or reperfusion, was correlated with observed microinfarction in the corresponding posterior region of the left ventricle.

Open Chest Preparation

The open chest experiments utilized sequential myocardial biopsy specimens taken from the ischemic and nonischemic regions of the left ventricle. Myocardial biopsy specimens were obtained serially up to 4 hours after coronary occlusion.[9]

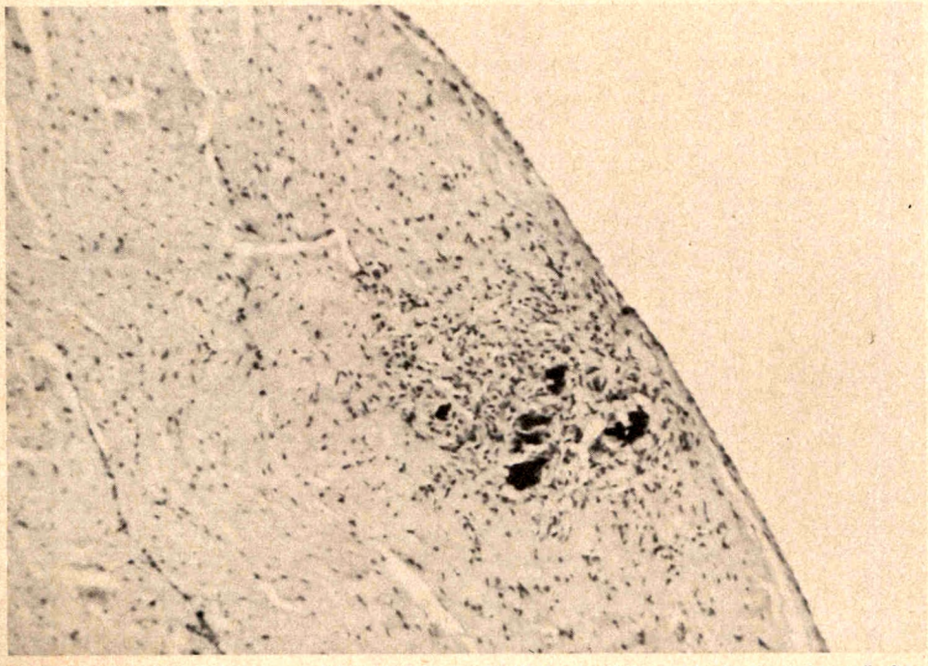
We used the Travenol TRU-CUT biopsy needle which, to our knowledge, has not previously been employed for heart biopsies. This needle caused minimal cardiac trauma and generally provided an intact biopsy cylinder of transmural cardiac tissue from which excellent micromorphologic specimens could be prepared. The tissue samples were microscopically surveyed with traditional hematoxylin-eosin stain and glycogen (Best-Carmine) stains. The glycogen content of the myocardial biopsy core was measured by its tinctorial presence in muscle fibers. Its grading ranged from full complement present in all fibers (4+) to total absence (0+). Grading was 1+ when glycogen was present in less than 25 percent of muscle fibers, 2+ when present in less than 50 percent, 3+ if found in more than 50 percent, and 4+ if found in more than 75 percent of fibers.

Results

The results from the closed chest dog series are reported in terms of two observations: (1) correlation of focal infarction in the left ventricle posterior wall with the finding of deranged lactate metabolism in the nonoccluded region, and (2) histopathology of microinfarcts (Fig. 1 to 5).

Series A: 7 days of occlusion (six dogs): After acute occlusion of the proximal left anterior descending coronary artery, regional measurements revealed significant lactate derangements in the coronary-occluded region, but often also in the nonoccluded zone.[5–7,10] Lactate balance determinations up to the 7th day of occlusion indicated severe lactate derangements in the occluded region in all six dogs, and also sporadic abnormal lactate extraction (less than 20 percent) in the nonoccluded segment (posterior left ventricle) in four of these animals. Progressive alterations of regional myocardial lactate metabolism in the coronary-occluded and nonoccluded zones are illustrated in one representative experiment (Fig. 6).

Table IA (series A) presents the histopathologic findings in various segments of the hearts that had



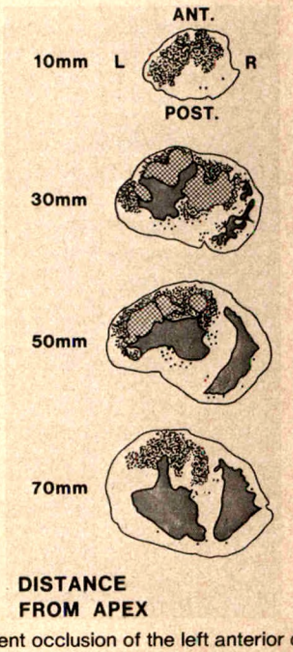


FIGURE 3, left. Photomicrograph of focal subendocardial infarct of left ventricular posterior wall after persistent occlusion of the left anterior descending artery for 7 days. Note the fibroblastic infiltration and granulation reaction with black areas representing calcification (hematoxylin-eosin ×250, reduced by 25 percent).

FIGURE 4, right. Method of infarct determination. The method described in the text is illustrated by segmental sketches of transcardiac slabs from the heart of a dog with 7 days of occlusion. Sections are 10, 30, 50 and 70 mm slabs, respectively, from the apex. Confluent infarction is represented by cross-hatching; the dots indicate minute foci of infarction. The latter are occasionally noted in the posterior interventricular septum and the posterior walls of the left and right ventricles. ANT. = anterior; L = left; POST. = posterior; R = right.

TABLE I
Myocardial Infarction Volume

Dog no.	Primary Infarct (cm^3)* (sum of LVAW, SAH, RVAH)	Infarction in Remote Area (cm^3)* LVPW	SPH	RVPH	Total
A. Series A, 7 Days of Occlusion					
161	54.9	6.4	0	1.7	8.1
191	76.5	0.7	1.2	1.0	2.9
232	66.9	1.6†	1.4	1.9†	4.9
238	30.0	0	0	0	0
411	30.4	0.2†	0.15	0	0.35
421	19.9	0.05	0.01	0.2	0.26
B. Series B, 7 Days of Reperfusion After 3 Hours of Occlusion					
168	21.4	1.7†	0.2†	0.5	2.4
188	39.2	0.5	0.2	0.03	0.73
220	15.3	1.3	0.2	0.8†	2.3
239	30.4	0	0.04	0.1	0.14
240	1.9	1.8	0†	0.03	1.83
250	10.4	0.9	0.3	0.05	1.25
287	1.4	0.4	0	0.05	0.45

* Sum of confluent and patchy infarction expressed in cubic centimeters of tissue.

† Observed small coronary embolic arterial occlusion.

AH = anterior half; AW = anterior wall; LV = left ventricle; PH = posterior half; PW = posterior wall; RV = right ventricle; S = septum.

TABLE II

Left Ventricular Posterior Wall Infarction vs. Derangements in Myocardial Lactate Extraction

Dog no.	Left Ventricular Posterior Wall Infarction (cm^3)*	Lactate Extraction (%)†	Correlation of Infarction vs. LE‡
A. Series A, 7 Days of Occlusion			
161	6.4	+1‡	Yes
191	0.7	−10‡	Yes
232	1.6	+16‡	Yes
238	0	+37	Yes
411	0.2	−4‡	No
421	0.05	+27	Borderline LE
B. Series B, 7 Days of Reperfusion After 3 Hours of Occlusion			
168	1.7	5‡	Yes
188	0.5	18‡	Yes
220	1.3	31	No
239	0	33	Yes
240	1.8	25	Borderline LE
250	0.9	22	Borderline LE
287	0.4	8‡	Yes

* Left ventricular posterior wall infarction expressed as tissue volume (cm^3).

† Lactate extraction (LE) is measured as $\left[1 - \frac{\text{regional venous lactate}}{\text{aortic lactate}}\right] \times 100\ (\%)$.

‡ Myocardial lactate extraction is considered significantly deranged when it is less than 20 percent.

been subjected to 7 days of occlusion of the proximal left anterior descending artery. "Remote area" myocardial infarction, largely of a focal character, was noted in the left ventricular posterior wall and also in the posterior aspects of the interventricular septum and right ventricle. The extent of these infarcts in individual segments is given as estimated volume in cubic centimeters of cardiac tissue. The average size of a "remote area" infarct was 2.8 cm^3 as compared with 46.4 cm^3 for an average primary anterior left ventricular wall infarct. In one animal the sum of remote infarctions was as large as 8.1 cm^3, which represents 4.4 percent of the total cardiac wall volume. There appeared to be no definite relation between volume of the microinfarcts in the posterior left ventricle and the size of the anterior wall infarct.

Figure 5 illustrates the dog hearts with the maximal and minimal observed "remote area" infarction for each group of animals. A detailed study of the vasculature revealed occasional instances of small arterial vessel occlusions within the posterior walls of the left and right ventricles. In one dog there was a possible geographic relation of the vascular lesion with the occurrence of remote microinfarction.

Table IIA (series A) contrasts the abnormal lactate metabolism measured in the nonoccluded zone of the left ventricle (for periods of at least 1 hour) against the finding of infarction in the posterior wall of the left ventricle. Of the total series of six dogs, five exhibited focal remote posterior wall infarcts in the left ventricle. Of these five animals four had instances of abnormal lactate metabolism (less than 20 percent) in the nonoccluded zone, one other dog had a marginal lactate extraction of 27 percent compared with a preocclusion control level of 51 percent, and 0.05 cm^3 of microinfarction. In the remaining animal with normal left ventricular posterior wall morphology, lactate metabolism was in the normal range. Thus, there was a direct correlation in five of the six animals between measurements of nonoccluded zone lactate balance and the presence or absence of remote infarcts (Table IIA). Similarly, myocardial potassium loss from the remote area correlated with the focal infarction.

Systemic vascular resistance, an index of left ventricular afterload, was determined during the 7 day observation period. Of four dogs that exhibited significantly increased systemic vascular resistance, three had evidence of remote infarction. Two animals with decreased or unchanged resistance had none or only 0.05 cm^3 focal necrosis in the posterior left ventricle. This suggests a strong correlation between increased afterload and finding of microinfarcts.

Series B: 7 days of reperfusion after 3 hours of occlusion of the left anterior descending coronary artery (7 dogs): The typical sequence of regional myocardial lactate measurements is indicated in an individual dog (Fig. 7). After coronary occlu-

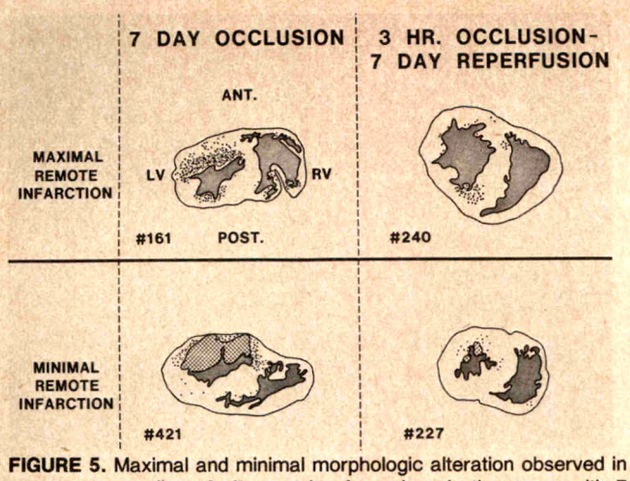


FIGURE 5. Maximal and minimal morphologic alteration observed in remote myocardium. **Left,** samples from dogs in the group with 7 days of occlusion. **Right,** samples from dogs with 7 days of reperfusion. All the sections shown were taken at similar levels of each dog heart. Each dot indicates (schematically) about 1 mm^3 of focal infarction; areas of confluent infarction are crosshatched. Animals 161 and 240 exhibit maximal observed remote area infarction in the left ventricular posterior wall of both groups of dogs. Animals 421 and 227 have minimal remote area infarction in the corresponding areas of heart. Primary and remote area infarctions in the reperfusion series were significantly less than those encountered in the continuously occluded series. LV = left ventricle; RV = right ventricle.

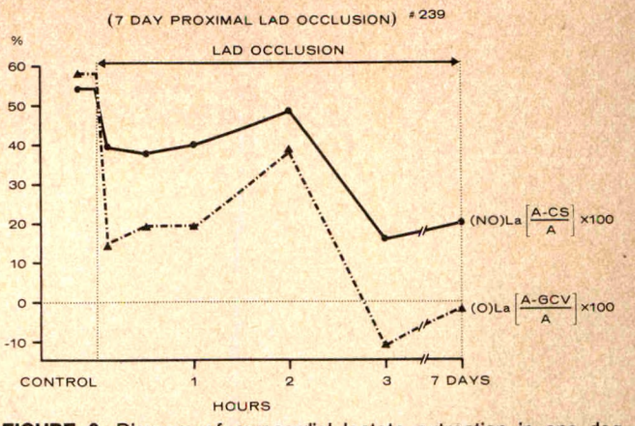


FIGURE 6. Diagram of myocardial lactate extraction in one dog measured by sampling blood draining the nonoccluded (NO, **solid line**) and occluded (O, **broken line**) segments during a control period, during 3 hours and after 7 days of occlusion of the left anterior descending coronary artery (LAD). Abnormal lactate metabolism (less than 20 percent) occurred not only in the occluded, but also in the nonoccluded myocardium. A = arterial; CS = coronary sinus; GCV = great cardiac vein; La = lactate.

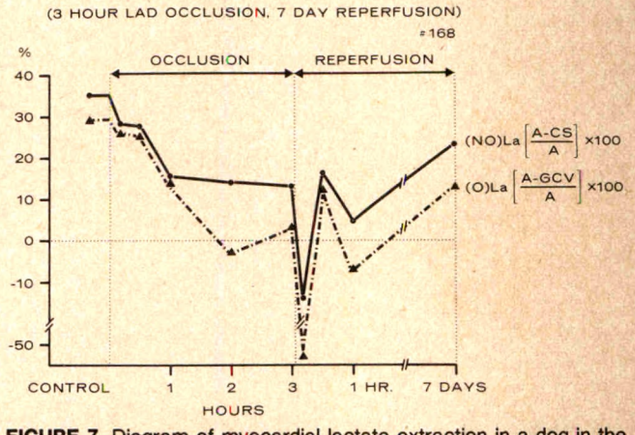


FIGURE 7. Diagram of myocardial lactate extraction in a dog in the group with 7 days of reperfusion after 3 hours of occlusion of the left anterior descending coronary artery (LAD). Lactate extraction was measured from blood draining nonoccluded (NO, **solid line**) and occluded (O, **broken line**) segments during the control period, 3 hours of occlusion, 1 hour of reperfusion and on the 7th day of reperfusion. Abnormal lactate extraction was noted in both occluded and nonoccluded myocardium during the occlusion period and early stages of reperfusion. On the 7th day of reperfusion, lactate extraction returned toward normal level in the nonoccluded area but remained depressed in the occluded segments. Abbreviations as in Figure 6.

sion, blood lactate balances became abnormal in both occluded as well as nonoccluded regions. This metabolic dysfunction tended to persist throughout the 3 hours of occlusion. The early (1 hour) period of reperfusion resulted in severe lactate imbalance and was characterized by arrhythmias and metabolic dysfunction persisting in both myocardial zones. However, after 7 days of reperfusion, six of the seven animals exhibited normal myocardial lactate balances in both zones.

Table IB (series B) summarizes histopathologic data in differing segments of hearts subjected to 7 days of reperfusion after occlusion of the proximal left anterior descending artery. Foci of myocardial infarction were observed in the posterior portions of the left ventricle and interventricular septum as well as the right ventricle (Fig. 5). The average remote area infarct was 1.3 cm^3 compared with an average primary infarct of 17.1 cm^3 in the anterior wall of the left ventricle. The largest sum of "remote area" infarction was 2.4 cm^3 and represented 0.9 percent of the total cardiac wall volume. As in group A, there appeared to be no strong correlation of these "remote area" infarcts with the volume of anterior wall infarct. Instances of small arterial occlusions were encountered in the posterior aspects of the septum or ventricle walls in four of the seven reperfused hearts, but none could be related to the geographic area of infarction.

Table IIB compares the nonoccluded myocardial blood lactate balance derangements with "remote area" infarction after 3 hours of occlusion of the left anterior descending coronary artery and 7 days of reperfusion. In this series of seven dogs posterior left ventricular wall focal infarction was present in six animals, of which three experienced abnormal lactate extraction (less than 20 percent) in the nonoccluded zone and the remaining three had lactate extraction of 22, 25 and 31 percent as compared with control values of 48, 59 and 49 percent, respectively. A history of normal or abnormal lactate metabolism correlated directly with posterior left ventricular configuration in four of the seven dogs, but since lactate extraction values approached the 20 percent level in two other animals, this correlation may be even more pronounced (six of seven dogs). Myocardial potassium loss from the remote area correlated with findings of focal infarction in all dogs of this series.

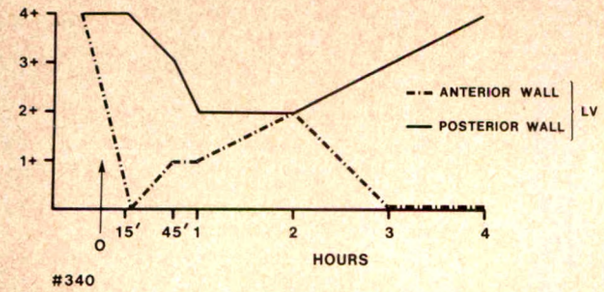


FIGURE 8. Tissue glycogen content obtained from anterior (occluded segment) and posterior (nonoccluded segment) walls of the left ventricle (LV) during 4 hours of coronary arterial occlusion.

Histopathologic study of remote myocardial infarcts revealed quantitative, but no basic qualitative difference between series A (7 days of occlusion) and series B (3 hours of occlusion and 7 days of reperfusion). The focal infarctions were predominantly (but not exclusively) subendocardial, varied widely in distribution and occurred singly or in clusters in remote areas of myocardium of both left and right ventricles (Fig. 5). The necrotic muscle fibers within the smaller infarcts were found to be replaced by young granulative tissue (Fig. 1). The larger remote infarcts manifested histiocytosis, fibroplasia, neocapillary formation and residual necrotic muscle fibers (Fig. 3).

Series C: 7 day sham preparation (three dogs): All catheters and instrumentation were installed in three dogs and typical manipulations were performed as in series A and B except that there was no intracoronary balloon occlusion of the left anterior descending coronary artery. After 4 hours of frequent measurements of cardiac function, the dogs were maintained in the vivarium. Measurements were repeated on the 7th day and the animals were then killed.

The microscopic examination in these sham dog hearts revealed no myocardial infarcts, or any significant deterioration of myocardial metabolic function as was noted in dogs with acute coronary occlusion with or without subsequent reperfusion (series A and B). No vascular lesions were noted.

Series D: open chest preparation—serial left ventricle biopsies during occlusion of the left anterior descending coronary artery (seven dogs) and in sham experiments (three dogs): Figure 8 indicates cardiac muscle glycogen changes in a selected dog with 4 hours of coronary occlusion. At 2 hours of occlusion sequential cardiac biopsies of the posterior left ventricular wall (remote area) show a reduction in glycogen content from 4+ (control) to 2+, and a subsequent gradual return to normal in spite of persisting occlusion of the left anterior descending coronary artery (Fig. 9). In the coronary-occluded region (nonremote area), glycogen content was reduced to zero in 15 minutes. Thereafter, there was a temporary and partial return of glycogen in this zone, but after 3 hours of occlusion there was again a complete loss of visible glycogen stores.

In four of the seven dogs with 4 hours of coronary occlusion, transmural tissue biopsy specimens taken from the posterior left ventricle indicated a reduction in glycogen from 4+ (control) to 2+ (Fig. 8). Left ventricular posterior wall glycogen measured over an equivalent period in the sham-operated dogs (without coronary arterial occlusion) exhibited no significant fluctuations.

Discussion

Remote Focal Infarction and Ischemia

Our new investigations disclosed distinct ischemic alterations of metabolic and mechanical function and focal infarction of muscle in the corresponding remote areas of myocardium. Such remote lesions were commonly noted after occlusion of the left anterior descending coronary artery for 7 days and also after reperfusion following 3 hours of coronary occlusion.

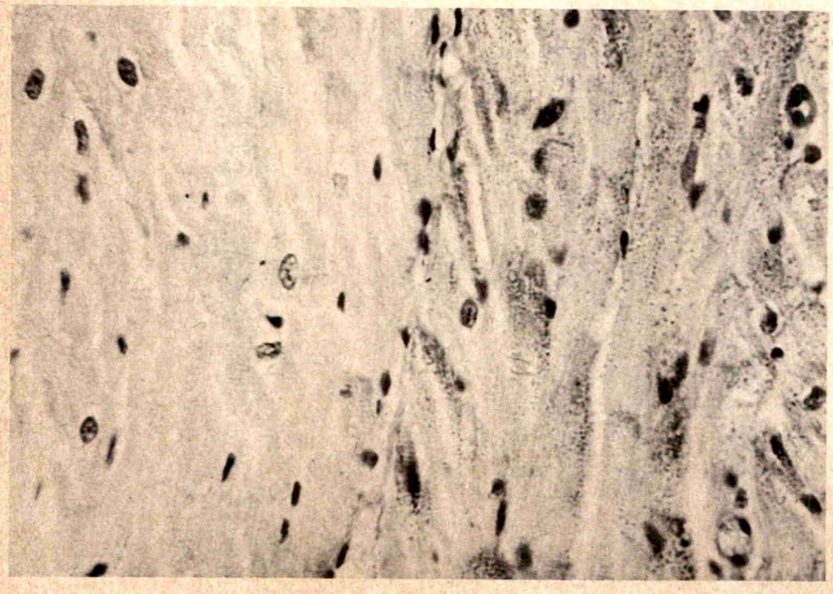


FIGURE 9. Photomicrograph of myocardial biopsy specimen after 2 hours of coronary occlusion. At left, most of the fibers have lost their glycogen granules, whereas those on the right contain normal amounts of granular and cross-striated deposits of glycogen. Glycogen is red in such preparations and is not readily demonstrated in black and white photomicrographs. (Best-Carmine ×800, reduced by 33 percent).

In six dogs with 7 days of occlusion, five showed remote infarcts in the left ventricular posterior wall, and of the seven dogs with reperfusion for 7 days, six had such focal infarcts.

When the left anterior descending coronary artery was persistently occluded for 7 days the average primary infarct (anterior left ventricular wall) was 46.4 cm^3 compared with an average remote area infarct of 2.8 cm^3. In the reperfused series the corresponding average volume of infarction in the primary area was 17.1 cm^3 compared with 1.3 cm^3 in the remote area. The largest cardiac volume of remote area infarction of the series with 7 days of persistent occlusion was 8.1 cm^3 compared with 2.4 cm^3 in the group with reperfusion.

Thus, the data indicate that the average size of both the remote area infarct and the primary anterior wall infarct is substantially less in the group with 3 hours of occlusion and 7 days of reperfusion than in the group with 7 days of persistent occlusion.

A strong correlation was noted between the degree of such focal infarction and occurrence of abnormal lactate metabolism derived from the remote myocardium. Focal infarction was also noted in the right ventricle and the posterior interventricular septum. A histochemical analysis of the remote posterior myocardium revealed glycogen depletion in areas normally assumed to be uninvolved by coronary occlusion.

The question persists: How soon after coronary occlusion do these remote focal infarcts develop? We noted morphologic alterations characteristic of infarction in the remote posterior wall of a series of hearts removed after 3 hours of coronary occlusion (Fig. 2). Another question is whether prolonged reperfusion (7 days) after 3 hours of coronary occlusion limits or reduces the remote zone microinfarcts. Our data lead to the conclusion that 7 days of reperfusion did not modify the quality or character of focal infarction in remote areas, thus suggesting that the lesions caused by the coronary occlusion could occur in the first 3 hours of occlusion and that some were irreversible. However, the measured volume of remote area microinfarction was smaller in the reperfused series.

To ascertain whether the remote lesions were indeed induced by the coronary occlusion, a series of animals were fully instrumented but the coronary arteries not occluded and then studied over a period of 7 days. No evidence of focal lesions or significantly deranged lactate metabolism was found in the sham experiments without occlusion.

Glycogen depletion and ischemia: Glycogen depletion has been previously described in acutely ischemic myocardium.[11–14] Our investigations indicate that glycogen provides a useful histochemical marker of ischemia. Histochemical studies of sequential biopsy specimens from an acutely ischemic myocardial segment revealed that glycogen stores were sharply depleted within 5 to 15 minutes after an acute coronary occlusion.[9] Limited data presented in this study of the remote myocardium indicate that glycogen content in the nonoccluded zone was greatly reduced within 1 to 2 hours of occlusion of the left anterior descending artery. By contrast, cardiac tissue biopsy specimens in the sham experiments revealed only minor, nonsignificant glycogen fluctuations. Thus, the glycogen depletion noted in the remote myocardium after a coronary occlusion should be considered an indication that this allegedly normal tissue must also be involved in an ischemic process. We also noted a definite association of characteristic ischemic fiber degeneration and glycogen depletion, suggesting the latter could be a forerunner of irreversible damage. However, tissue glycogen depletion does not necessarily prove that the myocardial damage is irreversible, as indicated in other experimental studies in which reperfusion led to a return of stainable glycogen to near control levels.[9]

Contraction force in remote zones: Our studies of regional mechanical function using miniature strain gauges revealed that myocardial force in the nonoccluded myocardium in the remote area which is assumed to become hypercontractile actually was decreased or remained unaltered in about half of the animals studied.[15] Such loss of contraction of the supposedly noninvolved zone might be a further indication that localized ischemia had occurred in the remote zone. However, it might also signify that this segment is contracting against an additionally compliant "occluded" zone.

Do Regional Abnormal Lactate Measurements Indicate Focal Ischemia?

The question may be raised whether regional venous blood sampling in our closed chest intracoronary balloon occlusion-reperfusion model really established an ischemic metabolic process in the nonoccluded segment, or whether the measurements are primarily due to mixing of blood from the ischemic zone into the blood draining the remote segment. Our model temporarily separates the coronary venous drainage compartments by brief balloon occlusion of the great cardiac vein while blood samples are being withdrawn. As a result of the occlusion of the left anterior descending coronary artery, the flow and intravascular pressures within the occluded zone decrease and there may actually be a tendency for normal arterial blood from the nonoccluded region to flow into and dilute the samples from the occluded zone. It is more difficult to envision substantial reversed mixing. Our measurements indicate a significant difference between the occluded and nonoccluded zone samples, indicating a meaningful separation of coronary venous samples from the occluded and nonoccluded zones.[6,7] The correlation of focal remote infarction with metabolic dysfunction presented in this study constitutes strong evidence that metabolic derangements often supervened in the nonoccluded zone after acute coronary occlusion. This correlation also suggests that ischemic derangements established through localized blood sampling are meaningful and significant.

Causes of Remote Myocardial Ischemia

The microinfarcts can be considered permanent markers indicating that an ischemic process had taken place. The origin of the remote myocardial ischemic lesions remains to be elucidated. The lesions might result from multiple interrelated factors that ultimately affect the balance between myocardial oxygen supply and demand. The likely factors affecting the remote myocardium include: (1) catecholamine effects, (2) catecholamine-induced platelet aggregation, (3) hypercontraction, (4) alterations in left ventricular afterload and preload, (5) postocclusion dysrhythmias, (6) coronary angiospasm, (7) thrombotic or embolic coronary arterial lesions, (8) generalized myocardial edema, and (9) severe hypotension and shock.

Catecholamine effects: The injurious effects of catecholamines on cardiac muscle and their similarity to myocardial ischemic injury have long been known.[16–18] These effects include intramyocardial hemorrhages, edema, patchy areas of myofibrillar damage, round cell infiltration and proliferation of fibrous tissue in the heart. The focal infarcts that are observed in the remote myocardium after coronary occlusion resemble catecholamine-induced myocardial lesions.

It is generally known that acute coronary occlusion is followed by a sympathetic autonomic system response, reflected in part by an increased release of epinephrine and norepinephrine into the bloodstream.[19,20] This increased plasma level of norepinephrine is associated with a rise in heart rate and increased inotropism, which tends to maintain cardiac output despite decreased left ventricular stroke volume. The sympathetic response also causes a redistribution of blood flow and increased systemic vascular resistance.[21] The latter maintains blood pressure, but augments left ventricular afterload and increases myocardial wall stress, which in turn may tend to reduce myocardial perfusion, particularly in the subendocardial portions of the cardiac wall. Coupled with the added effects of catecholamines on platelet aggregation,[22] such mechanisms may be responsible for a disproportion between oxygen supply and demand in the nonoccluded zone that, if prolonged, would lead to the observed microinfarction. The catecholamine hypothesis for remote myocardial microinfarction may find support in the description of focal necrosis observed after catecholamine infusion[17,21–24] and in patients with pheochromocytoma.[25]

Platelet aggregation due to catecholamines: Several investigations[26–28] have indicated that stress-induced secretion of endogenous catecholamines leads to platelet aggregation, which may cause thrombosis in the coronary microcirculation. This requires further study.

Hypercontraction: Several reports have suggested that compensatory regional hypercontraction occurs in the nonischemic segment of the heart after acute coronary occlusion.[29–31] This increased mechanical activity has been ascribed to a postocclusion augmented sympathetic tone. Conversely, there are reports in which mechanical function in the nonoccluded zone was decreased after an acute coronary occlusion, presumably as a result of ischemia of the remote myocardium or contraction of the normal tissue against an additionally compliant ischemic segment.[32] We have recently developed a series of miniaturized myocardial gauges for localized measurement of left ventricular wall force, thickness and segmental length.[15] Our regional mechanical measurements during short occlusions of the proximal left anterior descending artery indicated that, in the presence of a large, reversibly injured dyskinetic ischemic segment, the nonoccluded zone responds with hypercontraction in about 50 percent of cases, whereas there is hypocontraction or little change from normal contraction in the remaining instances. Hypocontraction might be attributed to ischemia in the remote myocardium. The finding of microinfarcts in the remote posterior right ventricle, which does not generate major muscle tension, suggests that hypercontraction and increased muscle tension are not the sole causes for the remote ischemic lesions.

Alterations in left ventricular afterload and preload: Our data on hemodynamic measurements frequently indicated a slight increase in left ventricular end-diastolic pressure and also in systemic vascular resistance after acute coronary occlusion. A significant increase in resistance and left ventricular end-diastolic pressure is associated with increased ventricular wall stress and hence higher myocardial oxygen demands. However, there was no correlation between left ventricular end-diastolic pressure and the occurrence of remote zone microinfarctions. Although increased systemic vascular resistance helps to maintain systemic blood pressure, it represents an elevated left ventricular afterload. Of the six animals in series A (7 days of occlusion), systemic vascular resistance increased substantially in four, decreased in one, and in the remaining dog increased temporarily and then decreased. Of the four dogs with elevated resistance, three exhibited remote myocardial wall infarction; focal infarction was also noted in the dog in which resistance increased only temporarily. There was no microinfarction in the one dog in which systemic vascular resistance dropped after coronary occlusion. It is possible that elevated systemic vascular resistance increased oxygen demands considerably and contributed in part to the infarction of the nonoccluded segment.

Postocclusion or postreperfusion dysrhythmias: We attempted to correlate arrhythmias that supervened after coronary occlusion or after reperfusion with the occurrence of focal remote necrotic lesions, but the association could not be significantly related.

Coronary angiospasm: It has been postulated that an angiospasm of a coronary artery can be induced by an organic arterial lesion, cannulation during arteriography or other mechanical stimuli and pharmacologic influences.[33–36] Regardless of its pre-

cise origin, coronary angiospasm may contribute to relative reduction in coronary flow in the nonoccluded zone, which may already exhibit increased oxygen demands due to hypercontraction.

Thrombotic or embolic coronary arterial lesions: In this study, instances of occlusive arterial lesions were encountered in the remote and nonremote areas of the heart. Such small arterial and venous thromboses were more prevalent in the series with 7 days of reperfusion than in the series with 7 days of occlusion. However, we could associate arterial obstructive lesions with the location of the infarcted remote myocardium in only one dog in the latter group and none in the former group.

Generalized myocardial edema: We have confirmed recent observations indicating that substantial cardiac wall edema supervenes in both the occluded and nonoccluded myocardium after coronary occlusion and reperfusion (Fig. 2).[37,38] Such edema might increase intramyocardial stress and extravascular forces, causing mechanical obstruction of coronary reperfusion which, if prolonged, would contribute to ischemia of the remote myocardium.

Severe hypotension and shock: It has been reported that significant systemic hypotension caused by hemorrhagic or cardiogenic shock may result in subendocardial infarction in various segments of the cardiac wall.[39] This would be expected whenever the blood pressure and coronary perfusion are decreased without commensurate reduction in myocardial oxygen demands. We have previously noted patchy infarction in the nonoccluded zone when severe hypotension and cardiogenic shock followed left anterior descending coronary arterial occlusion and reperfusion.[5] However, in that series we could not resolve whether the observed infarcts were caused by the coronary occlusion and reperfusion as such. In this study hypotension did not supervene in any animal, thus indicating that such microinfarction of the remote myocardium was not due to decreased systemic pressure.

Implications of Study

Our new data indicate that a correlation exists between focal infarction and deranged lactate metabolism in the nonoccluded remote area of myocardium after occlusion or reperfusion of the proximal left anterior descending coronary artery. This correlation, coupled with myocardial glycogen depletion noted in the supposedly noninvolved segments, serves to validate our prior observations of abnormal remote regional metabolism and morphology. It suggests that ischemia of remote areas should be recognized clinically by means of regional metabolic measurements.

One might anticipate the largest remote infarction to be associated with the maximal primary infarct, but our data revealed no such correlation and remote microinfarcts were also found with small primary infarcts.

Although the mechanisms and significance of ischemic events in the remote area remain to be elucidated, our observations of deranged myocardial mechanical and metabolic function and morphology constitute important evidence that the assumed "uninvolved" myocardium may also become ischemic. Because sustained remote ischemia may lead to serious complications, such as cardiogenic shock or pump failure, monitoring and management of the jeopardized remote myocardium might be as important to the overall management as treatment of the primary ischemic zone.

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Myocardial Revascularization After Acute Infarction

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The purpose of this study was (1) to establish the maximal interval between the onset of ischemia and reperfusion that would permit a decrease in the size of infarction, and (2) to evaluate the relation between changes in infarct size and preservation of cardiac function. Studies were carried out in 19 dogs of which 13 had temporary (1 to 3 hours) occlusion of the left anterior descending coronary artery. The hospital course of 15 patients of whom 13 underwent myocardial revascularization within 8 hours of acute infarction was also reviewed. *In dogs,* the eventual pathologic infarct size was significantly reduced if reperfusion was performed within 2 hours of ischemia. After 2 hours of ischemia, the revascularized segment remained dyskinetic on angiographic assessment and cardiac function was depressed. After 3 hours of ischemia, in spite of a patent coronary artery, the extent of infarct and dykinesia was greater than during ligation of the left anterior descending coronary artery. *In patients,* small infarcts developed with revascularization performed more than 4 hours after infarction but with revascularization of the left anterior descending coronary artery the size of the dyskinetic area (as assessed with angiography) was similar to that in patients with a closed graft to the left anterior descending coronary artery but with a patent graft to its diagonal branch. In all patients after revascularization the extent of the left ventricular dyskinetic area was smaller and cardiac function was significantly better than in patients who did not receive revascularization for complete occlusion of the left anterior descending coronary artery. In spite of successful revascularization, electrocardiographic evidence of transmural infarction persisted postoperatively. It is concluded that reperfusion of an area of myocardium that has been ischemic for less than 2 hours in dogs or less than 4 hours in man may lead to a significant reduction in the extent of infarction as well as improvement in cardiac function. However, the revascularized area remains angiographically dyskinetic and electrocardiographically abnormal.

Previous experimental studies[1,2] and recent clinical reports[3] indicate that reperfusion of an area of myocardium after a few hours of ischemia can result in a significant reduction of the eventual size of infarct. The purpose of our research was to answer some important questions regarding the surgical treatment of acute myocardial ischemia and infarction by direct myocardial revascularization (reperfusion). First, we attempted to establish the maximal interval from ischemia to reperfusion that would permit clinically and angiographically successful revascularization with reduction in the size of infarct. Second, we attempted to evaluate the relation between the extent of cardiac muscle preserved and cardiac function. The studies were performed simultaneously in a group of dogs and in a group of patients who underwent myocardial revascularization after acute infarction. Brief reports[4–7] on the results of this work have been periodically published elsewhere.

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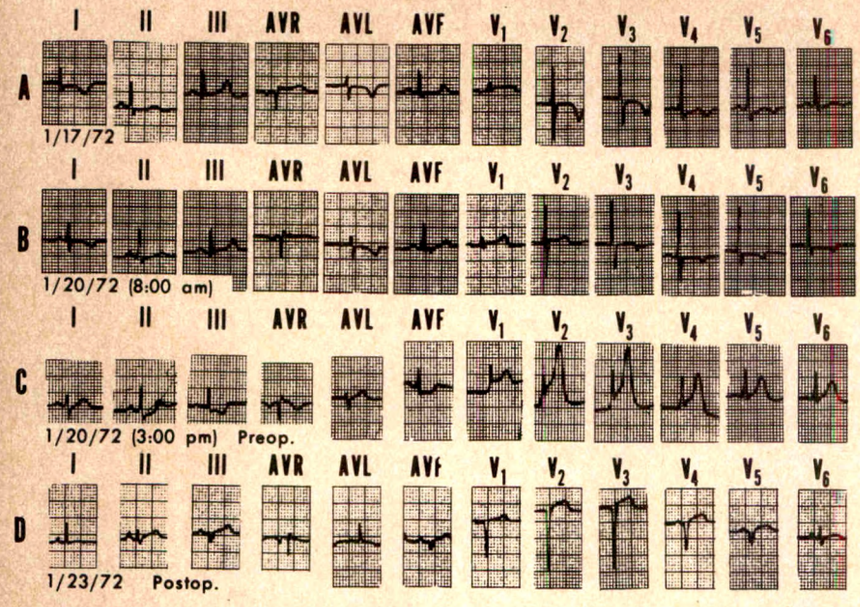

FIGURE 1. Case 6, Group II. Serial 12 lead electrocardiograms from a patient who was admitted with evidence of subendocardial ischemia **(A).** After 3 days of therapy, chest pain continued with persistent electrocardiographic changes **(B).** Diagnostic cardiac catheterization studies were performed at this time and within 3 hours there was acute S-T segment elevation in the precordial leads **(C)** concomitant with marked serum enzyme elevation. The patient was operated on within 6 hours and underwent myocardial revascularization within 8 hours of development of chest pain, sweating and hypotension. The postoperative electrocardiogram revealed evolution of anterior wall myocardial infarction **(D)** in spite of a patent anterior descending coronary graft (see Fig. 7). (Reprinted by permission from Bolooki et al.[13])

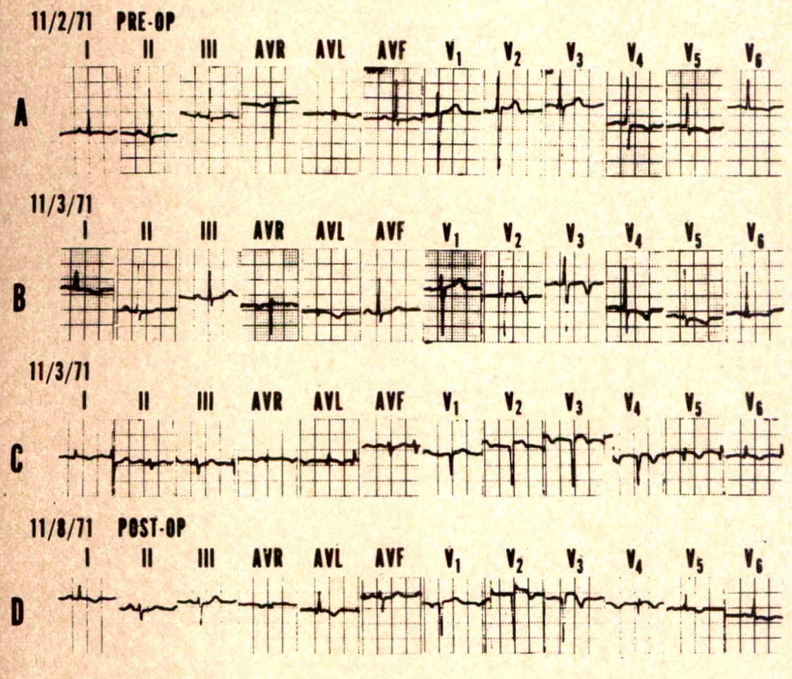

FIGURE 2. Case 9, Group III. Serial 12 lead electrocardiograms from a patient admitted with the diagnosis of preinfarction angina **(A).** In the course of 24 hours, the chest pain increased in frequency and severity in spite of extensive treatment. There was electrocardiographic evidence of subendocardial ischemia **(B).** The patient underwent emergency cardiac catheterization studies but within 2 hours presented with hypotension and sweating with electrocardiographic evidence of extensive anterior wall myocardial infarction **(C)** and serum enzyme elevation. He was operated upon immediately and received a bypass graft to the left anterior descending coronary artery within 4 hours of the onset of chest pain and electrocardiographic evidence of infarction. Postoperatively he remained in a low output state and required vasopressor therapy. An electrocardiogram taken 5 days postoperatively revealed further evolution of the anterior wall infarction **(D).**

Methods

Experimental Studies

Studies were performed in 19 mongrel dogs of both sexes weighing 23 to 25 kg. Preoperatively a control electrocardiogram, left ventriculograms and selective left coronary arteriograms were obtained. Cardiac catheterization was performed 3 to 4 days before surgical occlusion of the left anterior descending coronary artery followed by reperfusion of the vessel or by direct revascularization with the use of left internal mammary-coronary artery anastomosis.

Cardiac catheterization studies: These investigations were carried out under mild anesthesia with intravenously administered pentobarbital sodium (10 mg/kg body weight). With the dogs in the right anterior oblique position, a groin cut-down procedure was performed and a no. 7F Cordis catheter was threaded into the left ventricular cavity. A left ventriculogram was then obtained with hand injection of 20 cc of 90 percent Hypaque®. The left ventriculograms were recorded with Phillips equipment on 35 mm cine films at a rate of 60 frames/sec. Selective coronary arteriograms were obtained with use of a Cordis left coronary arterial catheter. By hand injection of 5 to 10 ml of 90 percent Hypaque into the coronary artery, the patency of this vessel and the extent of its collateralization and runoff were assessed.

Postoperative cardiac catheterization studies (ventriculography and left coronary and internal mammary artery arteriography) were performed 1 week after the operation using methods similar to those of the preoperative studies. In six dogs serial angiographic studies 2, 4 and 7 days postoperatively were performed to study the changes in left

ventricular contraction pattern and to assess patency of the left anterior descending coronary artery or internal mammary artery graft.

Surgical procedure: Surgery was carried out under pentobarbital sodium anesthesia (25 mg/kg) with the dogs intubated, connected to a Bird respirator and breathing an oxygen-air mixture. The dogs were placed in the right lateral decubitus position and prepared and draped in a sterile manner. The groin was dissected, and the femoral vein and artery were exposed. The vein was used for intravenous infusion, and the artery for intraventricular pressure monitoring by a transducer tip catheter (Edwards). A left thoracotomy was then made at the fourth intercostal space and the precordium was opened vertically to develop a cradle. The heart was examined, and communications between the left anterior descending coronary artery and the posterior branches were ligated. In 10 dogs, the left anterior descending coronary artery was ligated above the level of its first diagonal branch, and the left internal mammary artery, dissected free from the anterior chest wall, was used to anastomose to the left anterior descending coronary artery. In the remaining dogs the left anterior descending coronary artery was temporarily occluded (six dogs) or ligated (three dogs).

At a desired interval (ranging between 1 and 4 hours), the occlusion of the coronary artery or of the internal mammary artery graft was released. The revascularization procedure was performed without use of cardiopulmonary bypass but every dog received 10 to 15 cc/kg of low molecular weight dextran (Rheomacrodex®).

Patient Material

The subjects studied were 13 men and 2 women aged 42 to 64 years who were treated in the early stages of acute myocardial infarction. They were selected from among 20 such patients because of the location of a coronary lesion high in the left anterior descending coronary artery and because of availability of pre- and postoperative cardiac catheterization data. Thirteen of these 15 patients underwent myocardial revascularization. Two others did not consent to surgery but were included in this study as control subjects. Three of the 15 patients had acute infarction after cardiac catheterization for unstable angina pectoris. Two patients were admitted to the hospital early after an acute infarction. Seven patients experienced acute myocardial infarction just before scheduled coronary bypass surgery and three had an infarction in the course of administration of anesthesia for such surgery.

All patients had more than 80 percent obstructive lesions of the left anterior descending coronary artery at a site proximal to its first diagonal branch. One patient had a main left coronary lesion and two others had lesions in the right coronary artery as well. Complete preoperative hemodynamic data including cardiac catheterization studies were available in these patients. In the 13 patients who underwent myocardial revascularization, the interval between infarction and surgery ranged from 2 to 8 hours, but in each case, there was electrocardiographic evidence of acute transmural infarction of the anterior wall (Fig. 1 and 2). Electrocardiographic studies were repeated after the operation and for 3 consecutive days postoperatively. In addition, serum enzyme studies (creatine phosphokinase [CPK], hydroxybutyric dehydrogenase [HBD], lactic dehydrogenase [LDH] and glutamic oxaloacetic transaminase [GOT]) were performed in all patients before revascularization and were repeated on the day of operation and for 3 consecutive postoperative days.[8] All 11 patients surviving the revascularization procedure underwent cardiac catheterization studies at various intervals (4 weeks to 6 months) after the operation. Two patients each had two additional studies at 2 and 3 1/2 years after the operation.

TABLE I

Clinical Data in Four Groups of Patients

Case no.	Age (yr) & Sex	no. of Grafts/Grafts Open
Group I*		
1†	42M	2/LAD
2	47M	1/LAD
3	42M	2/LAD
4	56M	2/LAD-RCA
Group II*		
5	46M	1/LAD
6	52M	1/LAD
7	26F	1/LAD
8	38F	2/LAD-RCA
Group III*		
9	44M	2/Diag
10	39F	2/Diag
11	62M	2/Diag
Group IV*		
12†‡	48M	. . .
13†	56M	3/None
14†	47M	2/None
15‡	39M	. . .

* See text for composition of each group.
† Patient receiving circulatory assistance.
‡ Patient did not consent to operation.
Diag = diagonal branch of the left anterior descending coronary artery; LAD = left anterior descending coronary artery; RCA = right coronary artery.

Myocardial revascularization was performed under total cardiopulmonary bypass and mild to moderate hypothermia (32° to 28° C). The maximal period of total cardiac ischemia in the course of operation in any case was 5 minutes. Four patients had a single aortocoronary bypass graft to the left anterior descending coronary artery. Eight patients had two coronary grafts, one to the left anterior descending coronary artery. One patient had triple grafts, to the left anterior descending and circumflex coronary arteries and to a large diagonal branch.

Interval between infarction and revascularization: Depending upon the length of time from infarction to surgical revascularization and patency of the graft to the left anterior descending coronary artery, the 15 patients in the study were classified into four groups (Table I). Group I comprised four patients who were operated upon within 4 hours from the time of chest pain and electrocardiographic evidence of anterior wall infarction. Group II comprised four patients who were operated upon within 8 hours of myocardial infarction. Cardiac catheterization in this group was performed just before or during the course of infarction. Group III (three patients) underwent revascularization within 8 hours of infarction but were found to have occlusion of both the left anterior descending coronary artery and the graft to this vessel postoperatively. All three patients had a patent vein graft to the diagonal branch of the left anterior descending coronary artery. The preoperative cardiac catheterization studies in this group were performed *before* the episode of infarction. Group IV comprised four patients who were seen within 8 hours after acute anterior wall myocardial infarction; two of them re-

fused surgery and two others did not survive the operation. Hemodynamic studies in these patients were performed while they were undergoing diastolic augmentation with a balloon pump (Datascope).

Evaluation of Left Ventricular Performance

The left ventricular silhouette in systole and diastole in the right anterior oblique view was drawn and, with the projection factor calculated from the projected size of the catheter used for dye injection and its actual size, the left ventricular end-diastolic and end-systolic volumes were calculated. The area-length method of Dodge et al.,[9] was modified to the multiradii method and was used for this purpose by assuming the left ventricular cavity, for each bisection of the longitudinal axis, as an ellipsoid:

$$V = \pi 4/3\, L/2\, (M/2)^2 F$$

where L is the longitudinal axis of the inner left ventricular silhouette from midaortic valve area to the bisected mid-wall radius in the right anterior oblique view, M is the short axis of the left ventricle obtained from quadrisection of L by perpendicular lines, and F is the projection factor. Usually the longitudinal axis L was divided in half and again bisected to obtain two mid-wall sections of inner left ventricular chamber for data calculation.

In patients, the left ventricular volumes calculated from the right anterior oblique view were corrected for biplane cineangiography by using the formula:

$$V' = 0.95\, V\text{-}3$$

where V′ is the (biplane) volume of the left ventricle and V is the calculated volume from the right anterior oblique view.[10] Ejection fraction was calculated by subtracting the end-systolic volume from the end-diastolic volume and dividing the remainder by the end-diastolic volume.

Pressure data were calculated directly from the curves obtained by the transducer tip catheter (Millar, Houston). To obtain an index of left ventricular diastolic compliance (C), the method of Smith et al.[11] was utilized using the formula:

$$C = \Delta V/ESV/\Delta p$$

where ΔV is the stroke volume output from left ventricular angiograms, ESV = end-systolic volume and Δp is the change in diastolic pressure from end-systole to end-diastole. Cardiac output was measured by the Fick principle. The stroke work index (SWI) in g-m/m per m^2 was calculated from the formula:

$$SWI = \frac{(mBP - mRA)\, SI \times 1.336}{100}$$

where mBP and mRA are, respectively, the mean aortic and right atrial pressures in mm Hg, and SI is the stroke index in liters/min per m^2.

Evaluation of Infarct Size

In experimental studies: The dogs were killed after postoperative cardiac catheterization studies (7 to 10 days after the operation). The heart was then removed and patency of the left internal mammary coronary-artery anastomosis and the left anterior descending coronary artery was confirmed. The left ventricle including the septum was then dissected free from the right ventricular muscle, aorta and left atrium. The left ventricle was weighed and the area of infarct as seen grossly was excised by sharp dissection. The infarcted area was weighed and the percent infarct size in relation to left ventricular mass was obtained. Microscopic sections from the edges of the infarct and the adjacent left ventricular wall were obtained to assess the extent of inclusion of areas of healthy muscle within the infarcted segment and vice versa. With careful exclusion of the areas of healthy muscle from the infarcted area in previous studies we have been able to obtain a fairly accurate determination of the size of the area of infarct.[12]

In patients and in dogs: The extent of the border of the left ventricle that did not contract was calculated as described by Smith et al.[11] from the left ventricular silhouette in diastole and in systole in the right anterior oblique view. The extent of dyskinetic or akinetic left ventricular border was expressed as percent of the left ventricular silhouette in diastole. In four patients who died, the extent of infarct was assessed at autopsy by methods similar to those used in the experimental studies.

Results

Experimental Results

The period of ischemia for the 19 dogs ranged from 1 to 4 hours. Three dogs were found to have occlusion of an internal mammary artery graft and the left anterior descending coronary artery; these served as control dogs together with three other dogs with ligation of the left anterior descending coronary artery (Group IV). Of the remaining 13 dogs, 6 had 1 hour of ischemia before restoration of blood flow (Group I), 3 had 2 hours of ischemia (Group II) and 4 had 3 to 4 hours of ischemia (Group III).

Hemodynamic changes: Comparison was made of changes in left ventricular end-diastolic volume, end-systolic volume and ejection fraction before and after reperfusion (Table II). The data indicated a significantly depressed left ventricular performance postoperatively in dogs of Groups II, III and IV. There was no significant hemodynamic change in dogs with 1 hour of ischemia (Group I). At the time of postoperative studies (7 to 10 days after infarction) in dogs with reperfusion after 2 hours of ischemia (Group II) the end-diastolic volume had increased and ejection fraction had decreased significantly ($P < 0.05$). As compared with dogs in Group IV, dogs in Group III had larger end-diastolic and end-systolic volumes ($P < 0.05$) but there was no significant difference in ejection fraction between the two groups (Table III). The average size of infarct on pathologic study and the extent of dyskinetic area determined angiographically correlated well in dogs in Group IV only. In dogs in Groups I, II and III with revascularization after 1, 2 and 3 hours, respectively, the angiographic dyskinetic area was significantly larger than the pathologic infarct size.

Size of myocardial infarct: Pathologic studies showed that in dogs in Group I the size of the myocardial infarct 1 week to 10 days after the insult was nil except in one dog in which the infarct was 8 percent of left ventricular mass (Table II). In dogs with 2 hours of ischemia (Group II) infarct size was 11.8 ± 4.1 percent (standard error). In dogs with 3 hours of ischemia the infarct size ranged between 29 and 32 percent (mean of 31 ± 0.7 percent). Dogs in Group IV (three dogs with ligation of the left anterior descending coronary artery and three with an occluded inter-

TABLE II

Experimental Data in Four Groups of Dogs

Dog	EDV (ml)		ESV (ml)		%EF		% Infarct*	% Dyskinesia†
	1	2	1	2	1	2		
Group I: Dogs with 1 Hour of LAD Coronary Occlusion								
1	45	40	30	16	32	58	0	0
2	45	33	20	19	55	42	0	0
3	14	31	9	18	37	41	0	16
4	89	75	57	54	35	27	8	26
5	28	24	10	15	63	37	0	7
6	41	35	17	19	58	44	0	0
Mean	44	40	24	23	46	41	2.8	12
±SE	10	7	7	6	5	4	2.8	5
P value	<0.20		<0.20		<0.20		...	...
Group II: Dogs with 2 Hours of LAD Coronary Occlusion								
7	47	42	40	18	57	46	12	47
8	36	17	57	5	72	45	19	36
9	18	63	50	42	33	19	4.5	18
Mean	33.7	40.7	49	21.7	54	36.7	11.8	33.7
±SE	8.45	13.3	4.9	10.8	11.4	8.8	4.19	8.4
P value	<0.20		<0.10		<0.05		...	...
Group III: Dogs with 3 to 4 Hours of LAD Coronary Occlusion								
10	51	85	17	70	66	19	29	47
11	44	40	12	22	71	43	31	34
12	44	42	16	33	63	20	32	36
13	47	69	26	54	43	22	32	50
Mean	48	53	18	45	61	26	31	40
±SE	3	10	2	21	5	5	0.7	4
P value	<0.20		<0.05		<0.01		...	...
Group IV: Dogs with LAD Ligation or Closed Grafts								
14	27	32	12	23	55	28	26	25
15	16	48	6	20	63	58	31	30
16	24	22	17	16	27	25	33	30
17	22	34	12	29	47	14	18	30
18	36	42	20	36	42	15	32	30
19	31	45	17	19	44	25	23	27
Mean	26	37	14	24	46	27	27	29
±SE	2	3.9	2	3	5	6	2	1
P value	<0.05		<0.02		<0.01		...	...

* Gross pathologic size of infarct in relation to left ventricular mass as measured at autopsy.

† Extent of left ventricular wall dyskinesia over the diastolic chamber silhouette.

1 = preoperative and 2 = postoperative angiographic data; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LAD = left anterior descending coronary artery; *P* = probability value in relation to pre- and postoperative angiographic data; SE = standard error.

TABLE III

Experimental Studies: Statistical Analysis of Postoperative Data

Groups Compared	EDV	ESV	% EF	% Dyskinesia	% Infarct
I with IV (df = 10)					
t score	0.274	0.060	1.833	9.366	4.549
P value	<0.20	<0.20	<0.05	<0.001	<0.001
II with IV (df = 7)					
t score	0.252	0.192	0.833	0.588	3.173
P value	<0.20	<0.20	<0.20	<0.20	<0.01
III with IV (df = 8)					
t score	1.889	1.907	0.0176	3.24	1.523
P value	<0.05	<0.05	...	<0.01	<0.10

df = degrees of freedom for *t* tests, indicating number of observations minus 1; other abbreviations as in Table II.

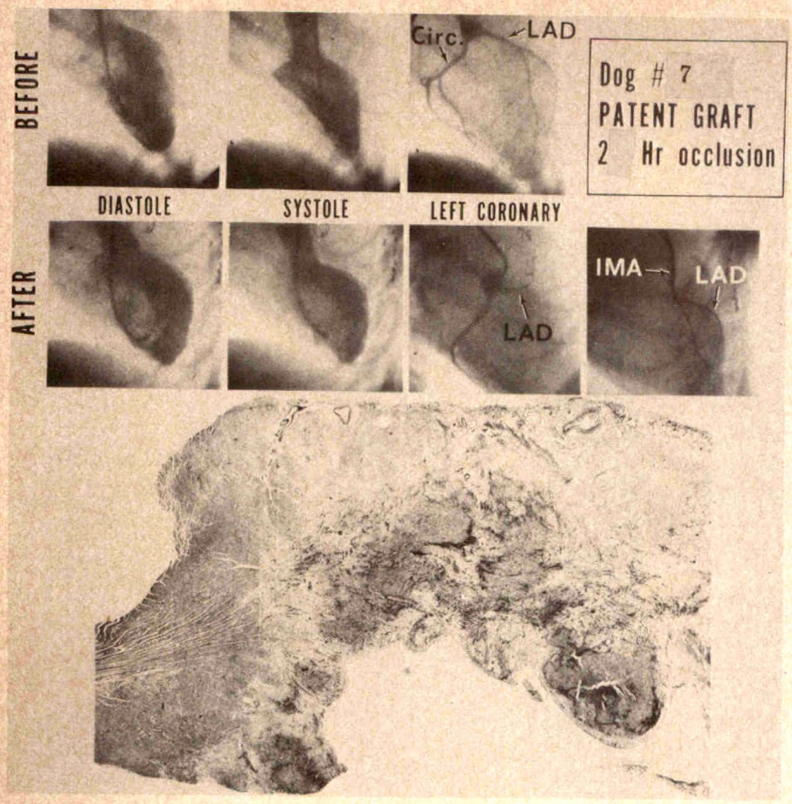

FIGURE 3. Dog 7. Comparison of the preoperative **(top)** left ventricular angiogram and postinfarction **(bottom)** left ventriculogram in a dog after 2 hours of coronary ischemia. The internal mammary artery (IMA) graft to the left anterior descending coronary artery (LAD) is patent, but the anterior wall of the left ventricle is dyskinetic. Microscopic view of a section of the anterior wall of left ventricle of this dog is shown below. (Hematoxylin-eosin ×5, reduced by 10 percent.)

nal mammary artery graft) had a mean infarct size of 27 ± 2 percent of the weight of the left ventricle (Table II).

Pathologic studies also revealed that 7 to 10 days after infarction in dogs in Groups I and II the infarct involved only the inner third of the left ventricular wall and superficial left ventricular fibers were preserved (Fig. 3). In dogs with 3 hours of ischemia, the infarct was transmural and usually included the interventricular septum. However, in dogs in Groups II (Fig. 3) and III, the anterior left ventricular wall was dyskinetic in spite of patency of the internal mammary-coronary artery anastomosis or of the left anterior descending coronary artery proper. As compared with dogs having reperfusion after 3 hours of ischemia (Group III with an infarct size of 31 ± 0.7 percent), dogs in Group IV had smaller infarcts (27 ± 2 percent) although this difference was not statistically significant (Tables II and III). However, there was a significant difference ($P < 0.01$) between the pathologic size of the infarct in dogs in Groups I and II compared with that in dogs in Group IV, whereas the extent of left ventricular dyskinesia differed significantly only in dogs in Groups I and IV (Table III). In comparison with dogs in Group IV, those in Group III had a larger dyskinetic area (40 ± 4 percent vs. 29 ± 1 percent, $P < 0.01$).

Serial angiographic studies on days 2, 4 and 7 after revascularization in four dogs in Group III and in two dogs in Group II failed to show any changes in the extent of left ventricular dyskinesia or in cardiac function (data not shown) from findings in the initial postoperative studies on day 2.

Clinical Results

Thirteen patients survived the operative procedure in the course of acute myocardial infarction. Postoperatively, three of these patients had severe cardiac pump failure and cardiogenic shock requiring vasopressor therapy (two patients) or intraaortic balloon counterpulsation for 48 hours (one patient).

The classification of the patients into four groups was based on the success of the revascularization procedure and the interval between operation and acute myocardial infarction as assessed by electrocardiographic and serum enzyme findings evaluated after the fact. Myocardial revascularization was considered successful if there was a patent vein graft to the left anterior descending coronary artery (Groups I and II). The zero time for development of infarction was the onset of chest pain that lasted for more than 30 minutes and that during its course was accompanied by evidence of infarction (serum enzyme changes and S-T segment elevation in the electrocardiogram). The duration of ischemia was from time zero to the time of completion of the vein graft anastomosis to the aorta and the left anterior descending coronary artery.

The four patients in Group IV died, the two not operated on within 3 to 5 days after acute myocardial infarction and the remaining two at surgery when they could not be weaned from cardiopulmonary by-

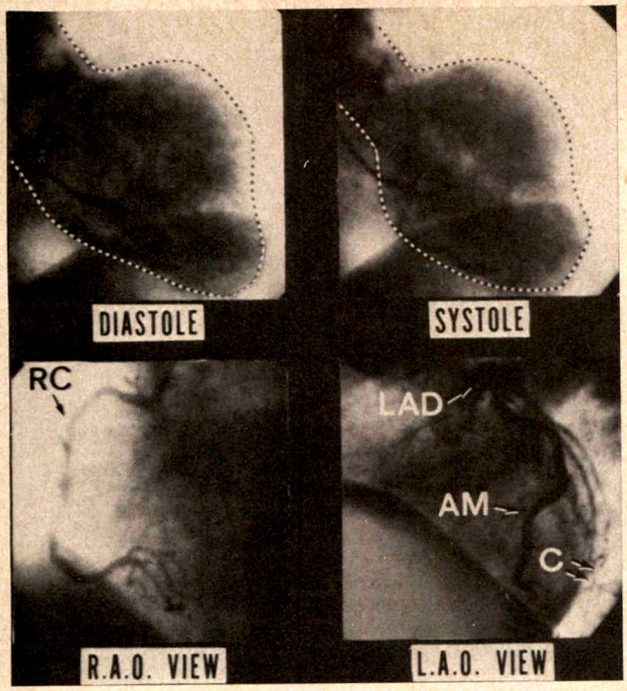

FIGURE 4. Case 12, Group IV. **Top,** left ventricular angiograms in diastole and systole in a patient with total acute occlusion of the left anterior descending coronary artery (LAD). The right coronary artery (RC) and the circumflex artery (C) with its acute marginal branch (AM) were patent. **Bottom,** coronary arteriograms in the right anterior oblique (R.A.O.) and left anterior oblique (L.A.O.) views. Cardiac catheterization studies in this patient were performed during intraaortic balloon assistance. Although the patient was studied within 8 hours of acute myocardial infarction, he refused surgical intervention and died 2 days later.

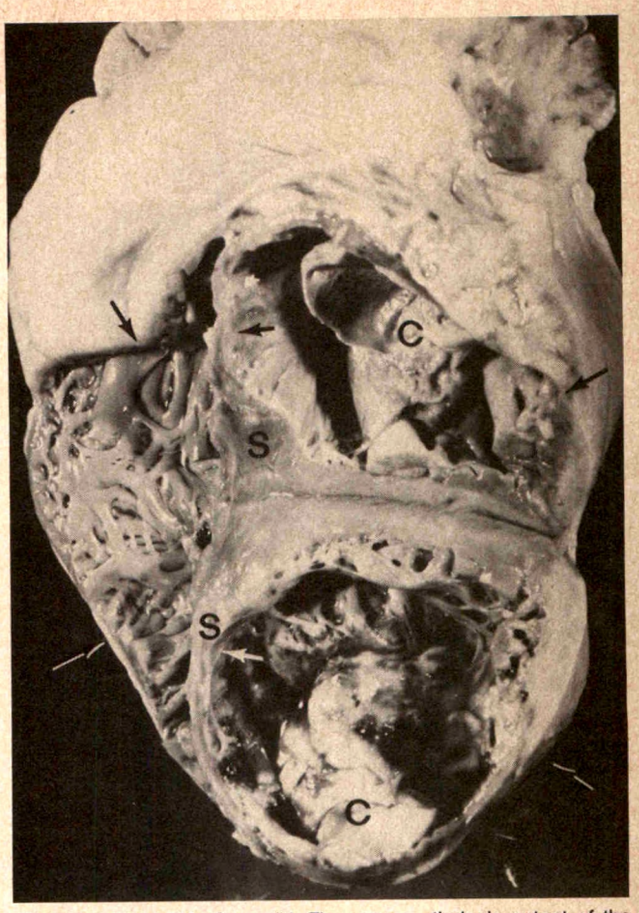

FIGURE 5. Case 12, Group IV. The gross pathologic extent of the acute myocardial infarct in the patient whose left ventricular angiograms are shown in Figure 4. The infarct involved 70 percent of the circumference of the left ventricle. The infarcted area **(between arrows)** is seen to have gelatinous degeneration and intracavitary clot formation (C). The left ventricular septum (S) and the right and left ventricular cavities are shown in a cross section from the middle of the infarcted area.

pass. At autopsy these patients had 61 ± 5 percent of the left ventricular mass involved in the process of infarction. A left ventricular angiogram from one of these patients (Case 12) is shown in Figure 4 and the pathologic photograph of myocardial infarction in this heart is shown in Figure 5.

The four patients in Group I received seven coronary bypass grafts, of which five were patent (Table I). The four patients in Group II had five coronary grafts, all of which were patent. Patients in Group III received six coronary grafts, of which only three were patent. Thus, the total number of grafts in these three groups of patients was 18 and the total number of patent grafts was 13, giving an overall patency rate of 72 percent. One patient in Group IV received triple coronary grafts and one a double coronary graft with myocardial infarctectomy. In both of these patients the coronary bypass grafts were technically feasible and at the time of autopsy the graft anastomoses with the coronary artery were patent. There was an overall operative mortality rate of 15 percent (2 of 13 patients).

Hemodynamic changes: Table IV presents the hemodynamic data for all patients. *In Group I* (myocardial revascularization within 4 hours of infarction), there was no significant change in most indexes. There was, however, a slight improvement in cardiac index and ejection fraction and a decrease in left ventricular end-diastolic pressure. *In Group II* (patients undergoing myocardial revascularization 4 to 8 hours after infarction with a patent graft to the left anterior descending coronary artery), there was no significant change in most indexes of cardiac function, but end-diastolic volume increased significantly postoperatively ($P < 0.05$). *In Group III* (patients undergoing myocardial revascularization within 4 hours of infarction but with occlusion of the left anterior descending coronary artery and its graft and patency of a diagonal branch graft, there was a significant increase in left ventricular end-diastolic pressure (from 9 ± 0.8 [standard error] to 19 ± 2 mm Hg, $P < 0.05$). The preoperative cardiac catheterization data in this group of patients (Group III) were obtained before development of acute myocardial infarction since in all the infarct occurred just before scheduled elective coronary surgery. *Group IV* patients served as control subjects in order to evaluate the extent of left ventricular dysfunction and myo-

cardial infarction after complete occlusion of the anterior descending coronary artery. The preoperative cardiac catheterization studies in these patients indicated a marked depression of left ventricular function (Tables IV and V), and three of these patients underwent intraaortic balloon pumping in the course of cardiac catheterization (Table I).

Changes in infarct size: Except for Group I (patients who underwent myocardial revascularization within 4 hours after myocardial infarction and who had a patent graft to the left anterior descending coronary artery), all patients had a large area of left ventricular dyskinesia. In patients in Group IV, which served as a control group, the preoperative data indicated the presence of left ventricular dyskinesia involving 45 ± 6 percent (standard error) of the diastolic silhouette of the left ventricle. This extent of dyskinesia was greater than in all other patients (P <0.001) (Table V). Data comparing the extent of dyskinesia in patients in Groups I (patent graft to the left anterior descending coronary artery) and III (closed graft) revealed a significant difference in the postoperative extent of dyskinesia. In Group I only one patient had 5 percent dyskinesia of the left ventricle compared with a mean value of 20 ± 1 percent in patients in Group III (P <0.001) (Table IV). The extent of dyskinesia in patients in Group II (myocardial revascularization after 4 hours of infarction and a patent graft to the left anterior descending coronary artery—successful revascularization) was slight-

TABLE IV

Hemodynamic and Angiographic Data in Four Groups of Patients

	CI		EDP		SWI		% EF		EDV		ΔV/ESV/ΔP		% Dyskynesia†		
Patient	1	2	1	2	1	2	1	2	1	2	1	2	1	2	% Infarct*
Group I: Revascularization <4 Hours, LAD Open															
1	2.8	2.8	32	12	0.02	0.26	27	61	150	146	0.006	0.16	10	5	...
2	2.3	3.1	20	14	0.6	0.40	42	61	105	137	0.06	0.07	22	0	...
3	3.0	2.3	16	16	0.43	0.26	68	65	224	177	0.11	0.02	20	0	...
4	2.2	2.7	26	11	...	0.40	69	66	153	100	...	0.07	20	0	...
Mean	2.5	2.7	23	13	0.35	0.33	56	63	158	140	0.05	0.08	18	1.2	...
± SE	0.19	0.16	3	1	0.17	0.04	13	1	24	15	0.03	0.02	2	1.2	...
P value	<0.20		<0.10		<0.20		<0.20		<0.20		<0.20		<0.01		...
Group II: Revascularization >4 Hours, LAD Open															
5	3.6	3.7	25	14	0.37	0.44	38	38	232	257	0.01	0.01	38	38	...
6	2.3	2.4	6	18	0.32	0.24	78	51	190	264	0.09	0.06	5	23	...
7	3.8	3.8	14	14	0.38	0.58	50	52	170	177	...	0.07	...	21	...
8	4.2	2.7	22	8	0.60	0.30	78	63	114	181	0.65	0.17	12	18	...
Mean	3.4	3.1	11	13	0.41	0.39	61	51	176	219	0.25	0.07	18.3	25	...
± SE	0.4	0.3	5	2	0.06	0.07	10	5	24	23	0.20	0.03	10	4	...
P value	<0.20		<0.20		<0.20		<0.20		<0.05		<0.20		<0.20		...
Group III: Revascularization <4 Hours, LAD Closed, Other Grafts Open															
9	3.1	1.8	11	22	0.33	0.20	...	40	...	250	...	...	0	20	...
10	2.2	2.1	8	22	0.40	0.22	65	50	82	134	0.20	0.02	0	18	...
11	2.2	2.4	10	15	0.25	0.29	76	40	223	305	0.06	0.01	0	22	...
Mean	2.5	2.1	9	19	0.32	0.23	70	43	152	229	0.13	0.01	0	20	...
± SE	0.2	0.1	0.8	2	0.04	0.02	5	3	70	50	0.06	0.004	0	1	...
P value	<0.20		<0.05		<0.20		<0.20		<0.10		<0.20		<0.001		
Group IV: Control, LAD Closed, Anterior Wall Infarction >4 Hours															
12	1.4	...	42	...	0.03	...	25	...	253	...	0.004	...	62	...	70
13	2.1	...	20	...	0.24	...	41	...	245	...	0.008	...	50	...	60
14	2.4	...	30	...	0.13	...	30	...	200	...	0.008	...	30	...	50
15	1.1	...	20	...	0.04	...	30	...	250	...	0.004	...	40	...	55
Mean	1.7	...	28	...	0.11	...	31	...	237	...	0.006	...	45	...	61
± SE	0.3	...	5	...	0.03	...	3	...	12	...	0.001	...	6	...	5

* Gross pathologic size of infarct in relation to left ventricular mass as measured at autopsy.

† Extent of left ventricular wall dyskinesia over the diastolic chamber silhouette.

1 = preoperative and 2 = postoperative data; CI = cardiac index (liters/min per m²); ΔV/ESV/ΔP (units) = compliance[11]; EDP = left ventricular end-diastolic pressure (mm Hg); EDV = end-diastolic volume (ml); EF = ejection fraction; ESV = end-systolic volume; LAD = left anterior descending coronary artery; P = probability (comparing pre- and postoperative data); SE = standard error; SWI = stroke work index (g-m per m²).

ly larger than in patients in Group III, who had a closed graft. In group II there was a mean dyskinetic area of 25 ± 4 percent compared with a mean value of 20 ± 1 percent in Group III (Table IV). This difference was not statistically significant (P <0.20), thus indicating the similarity of the extent of left ventricular dyskinesia and possibly infarction in patients undergoing revascularization of the left anterior descending coronary artery 4 to 8 hours after infarction, and those with revascularization of only its diagonal branch. The left ventricular angiograms from two patients in Groups II and III are shown in Figures 6 and 7.

Electrocardiographic changes: The electrocardiographic evidence of transmural infarction in all patients remained unchanged (Fig. 1 and 2). Evolution of infarction in the postoperative tracings was seen with persistent Q waves throughout the precordial leads and leads I and aVL.

Serum enzyme changes: Preoperative serum enzyme studies in 11 patients showed an increase in creatine phosphokinase to 1,200 ± 300 IU (standard error) (normal 150 IU); values for HBD, LDH and GOT were within normal limits. Postoperatively serum CPK increased markedly in all patients to a mean (13 patients) of 2,400 ± 700 IU, associated with increases in HBD, LDH and GOT for 3 to 4 days after revascularization. The peak increase in serum CPK occurred 12 hours after revascularization (Fig. 8).

Follow-up: In the course of 1 to 4 years of follow-up 11 patients have remained asymptomatic, and 9 of these have returned to work. Two patients from Group II are not working. Two other patients (one each from Groups I and II) were asymptomatic but died suddenly 4 months and 1 year, respectively, after operation with cardiogenic shock and cardiac arrest due to sudden closure of the left anterior descending coronary artery graft.

Two patients from Group II underwent repeated cardiac catheterization studies after revascularization. In one patient the size of infarct (left ventricular dyskinesia) decreased markedly within 9 months postoperatively.[7] A third postoperative cardiac catheterization in this man showed no further changes in left ventricular contraction pattern. In the second patient, who had two postoperative hemodynamic studies, there was no change in the size of a left ventricular aneurysm that developed in spite of a patent graft to the left anterior descending coronary artery (Fig. 9). However, the patient's cardiac function showed some improvement 3 1/2 years after revascularization (left ventricular diastolic pressure decreased from 22 to 14 mm Hg and cardiac index increased from 2.2 to 2.7 liters/min per m^2).

Discussion

Previous experimental studies have shown that with reperfusion of an area of myocardial ischemia within 3 hours of coronary occlusion, the size of the myocardial infarct (as determined by release of CPK) decreases appreciably.[1,2] Reperfusion has been employed clinically in patients who were considered to be in a phase of preinfarction[13–15] or early infarction[16] or to have extension of an infarct.[17] It has been shown[18,19] that revascularization can be carried out with acceptable operative mortality and results in improved cardiac function and a reduced size of myo-

TABLE V

Clinical Studies: Statistical Analysis of Postoperative Data

Groups Compared	CI	EDP	SWI	% EF	EDV	ΔV/ESP/ΔP	% Dyskinesia
I with II (df = 6)							
t score	1.098	0.106	0.6979	2.319	2.806	0.056	5.135
P value	<0.20	<0.20	<0.20	<0.05	<0.02	<0.20	<0.001
I with III (df = 5)							
t score	2.648	2.483	1.917	5.558	1.697	2.198	11.02
P value	<0.02	<0.05	<0.10	<0.001	<0.10	<0.05	<0.001
II with III (df = 5)							
t score	2.699	1.980	1.902	1.255	0.178	1.845	1.086
P value	<0.02	<0.10	<0.10	<0.20	<0.20	<0.10	<0.20
I with IV*(df = 6)							
t score	2.850	2.760	3.474	8.757	4.814	2.536	6.355
P value	<0.02	<0.02	<0.01	<0.001	<0.001	<0.02	<0.001
II with IV*(df = 6)							
t score	3.036	2.580	3.104	3.181	0.646	2.133	2.501
P value	<0.02	<0.02	<0.02	<0.01	<0.20	<0.05	<0.02
III with IV*(df = 5)							
t score	1.017	1.455	2.268	2.493	0.141	1.757	3.671
P value	<0.20	<0.20	<0.05	<0.05	<0.20	<0.10	<0.01

* In Group IV the patients died and had no postoperative studies; their preoperative data were used for statistical comparison.

Abbreviations as in Tables III and IV.

cardial infarct. Although, in clinical cases, it has been difficult to calculate the extent of decrease in size of the eventual infarct, it was postulated that reversal of the clinical shock state and improvement in cardiac function were indicators of a decrease in the area of nonfunctioning myocardium and, hence, of a decrease in the size of the infarct.

Effect of reperfusion on infarct size: Because of the complicated clinical setting in which emergency myocardial revascularization for an acute myocardial infarction is decided upon, it is not possible to categorize all patients into one group. For this reason we have classified our patients into four groups on the basis of several variables. For example, unlike the reported results in other studies, our data were correlated with the postoperative angiographic findings because operative survival or reversal of the shock state as such does not necessarily indicate a successful revascularization. Furthermore, in the clinical setting timing of the duration of ischemia or infarction has always been difficult. As a result, in all clinical studies related to this subject (including this investigation) there have been some departures from a strict research protocol that might affect the results considerably. To clarify our results we analyzed data in a group of patients selected because they had a similar anatomic lesion in the left anterior descending coronary artery and a similar interval between the onset of infarction and revascularization. To complement the clinical study, because the extent of pathologic infarction in patients could not be evaluated, we performed some experiments in dogs. We believe that the results show clearly that reperfusion of an ischemic (or infarcted) area of the myocardium can be performed with acceptable mortality and is beneficial in man if carried out within 4 hours of the onset of myocardial infarction. Our experimental studies indicated that, with reperfusion of an infarcted area within 2 hours of coronary occlusion, it was possible to decrease the eventual size of the infarct by about 50 percent (from 27 ± 2 percent to 11.8 ± 4.19 percent, $P < 0.001$). The data in four patients also indicated that when myocardial revascularization was carried out within 4 hours of infarction, the extent of

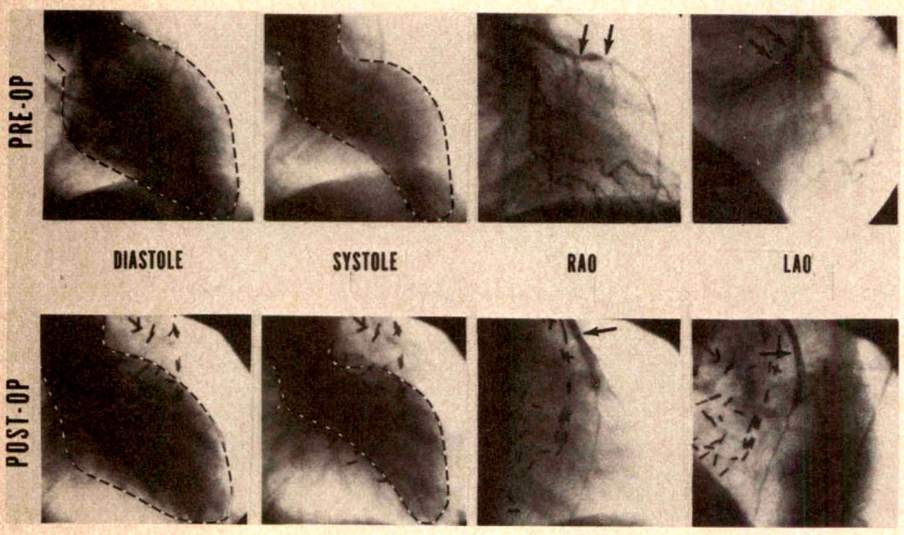

FIGURE 6. Case 5, Group II. Left ventricular angiograms **(left panels)** and coronary arteriograms **(right panels).** The preoperative anterior ventricular wall dyskinesia was due to multiple lesions in the left anterior descending coronary artery **(double arrows, top right).** Postoperative angiograms obtained 3 months later showed no change in the extent of anterior wall dyskinesia or ejection fraction (Table IV). The graft to the anterior descending coronary artery **(single arrow, lower panels)** is patent. There are multiple silver clips in the postoperative angiograms.

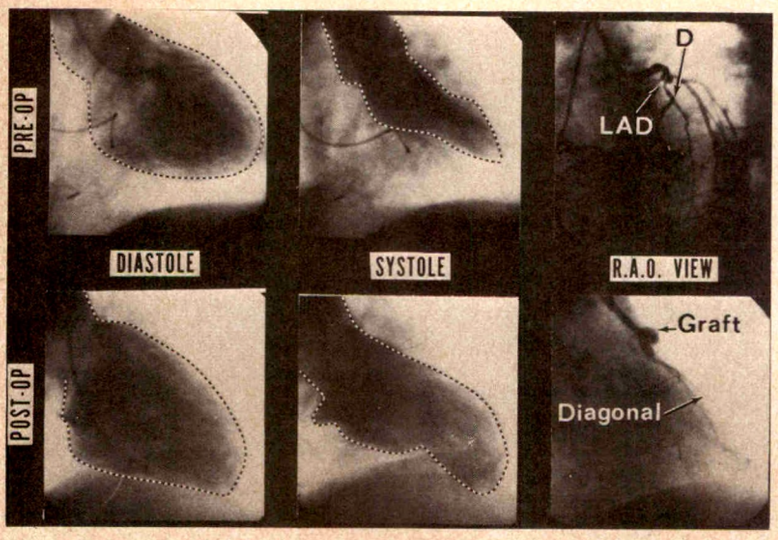

FIGURE 7. Case11, Group III. Pre- and postoperative left ventricular angiograms **(left and center panels)** and coronary arteriograms **(right panels).** The patient was studied before development of acute myocardial infarction. There was no left ventricular dyskinesia, but the left anterior descending coronary artery (LAD) and diagonal branch (D) showed more than 90 percent obstructive lesions. Acute myocardial infarction developed in this patient at the time of anesthesia induction as evidenced by electrocardiographic change and hypotension. Coronary grafts to the left anterior descending coronary artery and its diagonal branch were performed, and the patient tolerated the procedure well. Postoperative angiograms obtained 4 months later showed evidence of dyskinesia and aneurysmal formation of the anterior wall due to closure of the graft to the left anterior descending coronary artery. The graft to the diagonal branch was patent. (Reprinted from Bolooki et al.[7] by permission of the American Heart Association.)

left ventricular dyskinesia decreased considerably (from a mean value of 18 percent to 1.2 percent, $P < 0.01$).

Effect of reperfusion on cardiac function: A comparison of results of the effects of myocardial reperfusion on cardiac function produced less striking results. In dogs, myocardial revascularization within 2 hours decreased the extent of infarction but had a minimal effect on the extent of the angiographic dyskinetic area of the left ventricle. Furthermore, in these animals, myocardial reperfusion did not improve values for ejection fraction or left ventricular end-diastolic volume. Since the pathologic extent of myocardial infarction was to be decided within 7 to 10 days of infarction, all dogs were killed at that time and no long-term postoperative cardiac function studies were made. It is possible that the timing of these studies was responsible for some of our results as suggested by a previous study by Pairolero et al.,[20] who evaluated long-term changes in ejection fraction due to myocardial infarcts of various sizes.

In our patients, the postoperative studies after myocardial revascularization revealed some improvement in cardiac function in subjects who were operated on within 4 hours (Groups I and III). As indicated, the postoperative stroke work index in patients undergoing revascularization (reperfusion) of the left anterior descending coronary artery was higher ($P < 0.02$) and ejection fraction better than in those (Group III) who did not undergo such reperfusion. Yet four patients (Group II) who underwent myocardial revascularization more than 4 hours after infarction had a dyskinetic area corresponding to 25 percent of the left ventricular diastolic silhouette that was larger than the 20 percent dyskinetic area in the three patients (Group III) whose graft to the left anterior descending coronary artery was closed. However, each of these three patients had a patent graft to the diagonal branch of the left anterior descending coronary artery. Thus, we believe that the presence of an adjacent patent coronary graft contributed to limiting the extent of myocardial infarction in these patients. In patients with a patent graft (reperfusion) to the left anterior descending coronary artery, the anterior descending artery was the major anterior wall artery without a large diagonal branch or other collateral vessels. Although this anatomic variation could have played an important role in survival of these patients, it is safe to conclude that myocardial reperfusion performed more than 4 hours after myocardial infarction does not prevent development of a dyskinetic area of the left ventricle or an aneurysm (Fig. 7 and 9). In this study, we found no dyskinetic areas in three patients who underwent myocardial revascularization within 4 hours of electrocardiographic infarction. In these patients electrocardiographic

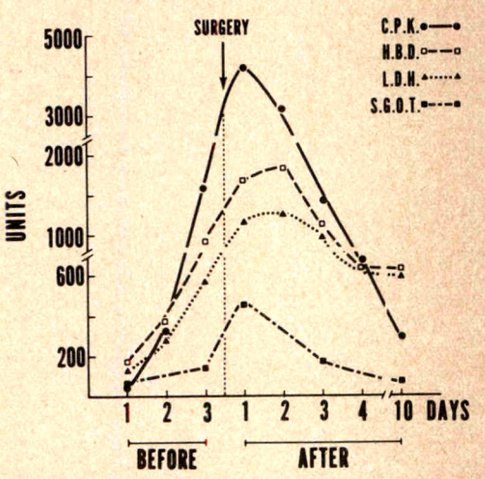

FIGURE 8. Case 9, Group III. Serum enzyme curves before **(top)** and after **(bottom)** myocardial revascularization. Preoperative studies were obtained on admission (1), during day 1 in the hospital (2) and before surgical intervention (3). The postoperative studies were performed on days 1 to 10 postoperatively. This pattern of serum enzyme rise and decline was seen in most patients operated on in the course of acute myocardial infarction.

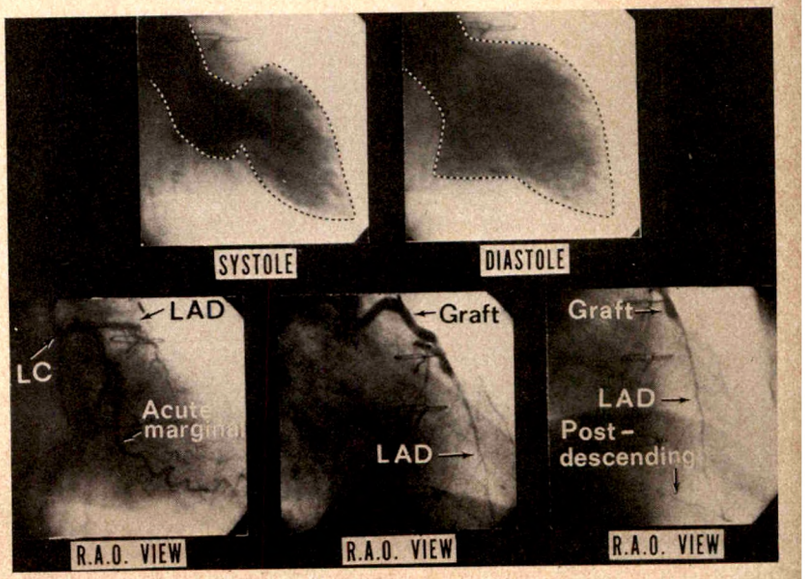

FIGURE 9. Case 6, Group II. Left ventricular angiograms **(top)** and coronary arteriograms **(bottom)** obtained 7 months postoperatively in the patient whose electrocardiograms are shown in Figure 1. A large left ventricular aneurysm involving the anterior and inferior walls has developed in spite of a patent graft to the left anterior descending coronary artery (LAD). The left circumflex coronary artery (LC) and its acute marginal branch are normal. A repeat cardiac catheterization in this man 3 1/2 years after revascularization of the infarct showed no changes in the pattern of left ventricular contraction. (Reprinted from Bolooki et al.[13] by permission.)

evidence of acute myocardial infarction (S-T segment elevation) and hypotension developed while they were being given general anesthesia in the operating room.

An interesting observation was the persistence of preoperative Q waves in the postoperative electrocardiograms (Fig. 1 and 2) in spite of successful revascularization of the infarct. This finding indicates that the revascularized transmural infarct remains abnormal electrophysiologically. In our experience with these and other patients with the so-called intermediate coronary syndrome or preinfarction angina, the only reversible electrocardiographic changes have been those of subendocardial ischemia (T wave inversion in precordial leads) regardless of the duration of these changes before operation.[13]

Clinical implications: Our study shows that the duration of ischemia before reestablishment of blood flow to the distal areas of an occluded coronary artery in man must be limited to 4 hours if reperfusion is to lead to improvement in cardiac function and a decrease in the extent of the infarct. This finding is supported by our experimental results, although perhaps because of the acute conditions of the experiments, the time limit in dogs is 2 hours. This difference in time may also indicate a greater tolerance of human myocardium to ischemia and is most likely due to the presence of numerous intercoronary collateral communications and the insidious onset of coronary obstruction.

In addition to a significant decrease in the extent of dyskinetic area in patients who had successful myocardial revascularization (reperfusion) early after infarction, the overall cardiac function was better than in patients who underwent myocardial reperfusion late after infarction (Group II) or did not undergo revascularization of the left anterior descending coronary artery (Group III). However, long-term follow-up studies (1 to 4 years) in these patients demonstrated that, regardless of patency or closure of the bypass graft to the left anterior descending coronary artery, most patients undergoing revascularization for an acute infarct remained asymptomatic and many returned to their previous activities. Although a recent report by Shell and Sobel[21] indicates the advantages of noninvasive measures to reduce infarct size in patients with myocardial infarction, perhaps a study of matched groups of patients treated by noninvasive (antihypertensive) methods and by myocardial reperfusion would further our knowledge of the effects of each of these methods. It is likely, however, that no one method will be useful for all patients and in the future the patients may be carefully selected for a specific method of therapy.

Acknowledgment

We express our gratitude to Drs. Ali Ghahramani, Leonard Sommer and Stephen Mallon, who performed the cardiac catheterization studies in these patients. Drs. James Jude and Richard Robinson performed surgery in two of these patients. We also appreciate the data analysis and calculations by Miss Adrianne Fried, BSN.

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The Gastrointestinal Absorption of Organic Nitrates

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It has been nearly 100 years since William Murrell[1] of England treated his first anginal patient with nitroglycerin. He directed the patient to drop 3 drops of a 1 percent solution of nitroglycerin into 1/2 oz of water and take it three times daily. Murrel was impressed by the improvement in the patient's condition and his ability to abort an attack by swallowing a dose of his medicine. There is no doubt that an adequate therapeutic quantity of the drug was absorbed.

Until the advent of reserpine and other antihypertensive drugs, erythrityl tetranitrate (30 mg) and mannitol hexanitrate (15 mg) were used extensively in the treatment of hypertension.[2] There appeared to be no question concerning the absorption of either of these drugs. The hypotensive maximal action occurred within 1.5 hours and persisted for 5 to 6 hours. Although these two hypotensive agents have been largely abandoned, they have been replaced by antianginal drugs of the nitrate class such as isosorbide dinitrate and pentaerythritol tetranitrate. In addition, nitroglycerin has become available in sustained release forms, and this development has precipitated the question of the absorption of nitroglycerin when administered in this form rather than as a sublingual tablet.

This controversy appears to have originated from the extensive investigations of Needleman of the Washington University Medical School on the action of nitrates in animals. Needleman's work, supported by the American Heart Association, was reported to the *Wall Street Journal,* and the resulting publicity has caused patients to lose confidence in these drugs. The thrust of Needleman's thesis is summarized by him in a comment in the *Annals of Internal Medicine.*[3] He states: "Orally administered organic nitrates are absorbed into the portal circulation and are rapidly and completely degraded by a liver enzyme before reaching the systemic circulation and therefore can have little chance of producing vasodilation."

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We believe that a century of clinical data on the use of these agents in hypertension and coronary insufficiency disease indicates that this statement of Needleman's is not in accordance with the facts. Since this statement involves the use of mainly three drugs—isosorbide dinitrate, pentaerythritol tetranitrate and nitroglycerin in sustained release forms, we confine the refutation to these drugs.

1. Isosorbide dinitrate: One of us (J.C.K. Jr.) directed the synthesis of this agent and studied it first as a vasodilating agent. Several of us ingested tablets of the drug and in each case the blood pressure was reduced by an average of 20 percent. The hypotension persisted for 4 to 6 hours.[4]

Buckley et al.[5] showed that isosorbide dinitrate and pentaerythritol tetranitrate were active in producing depressor activity and decreased coronary vascular resistance when administered intraduodenally in dogs. They commented on the persistence of the action of isosorbide dinitrate. We[4] showed that this agent was resistant to hydrolysis in vitro.

2. Pentaerythritol tetranitrate: The literature on pentaerythritol tetranitrate is voluminous,[6] and numerous articles bespeak the activity of orally administered pentaerythritol tetranitrate. It has been shown by Davidson et al.[7] that radioactive carbon-14-labeled pentaerythritol tetranitrate entered the general circulation and was degraded to the tri- di- and mononitrates and finally to pentaerythritol. Davidson et al.[8] also showed that pentaerythritol tetranitrate may be considered a precursor of the more active pentaerythritol trinitrate that is formed in the liver by the cleavage of one nitrate group from the molecule.

After the oral administration of pentaerythritol tetranitrate to rats, pentaerythritol trinitrate was found in the plasma for 24 hours.[9] In addition, the trinitrate forms a glucuronide that is more refractory to degradation than pentaerythritol tetranitrate.[10] Pentaerythritol trinitrate glucuronide serves as a reservoir for its aglycone and remains in the blood 48 hours after pentaerythritol tetranitrate has been ad-

ministered. Cammarto et al.[11] showed that pentaerythritol trinitrate and nitroglycerin were effective as depressors when administered in the intraportal vein or intraduodenally in the dog and rat.

3. Sustained release nitroglycerin tablets: It is clear that sublingually administered nitroglycerin bypasses the portal circulation and thus prevents degradation by the liver. Despite the degradation of orally administered nitroglycerin, adequate therapeutic levels are probably available. To support this view we extrapolate to man the results of a study[12] made more than a decade ago:

The coronary vessels of the isolated rabbit heart (Langendorff preparation) were perfused with a known amount of nitroglycerin. The coronary flow increased about 50 percent, but only 14 percent of the drug was fixed by the receptor sites in the coronary vessels; the remainder appeared unchanged in the perfusate. Thus, it would appear that only a fractional portion of the dose of nitroglycerin is required to produce the maximal effect. This indeed may parallel what occurs in man when the sustained release tablet of nitroglycerin is administered. In a recent editorial, (one of us)[13] recorded several experiments performed in man to demonstrate the effectiveness of sustained release nitroglycerin tablets (Nitrong®). Two of these are recorded. Mason et al.[14,15] used a venous occlusion technique and showed definitive evidence of the peripheral activity of orally administered nitroglycerin. In the studies, dilation of the peripheral vessels led to pooling of the blood in the capacitance reservoir, thus decreasing the functional circulating volume. Sustained release nitroglycerin tablets provided activity for at least 7 hours as shown by pulse contour measurements.

Using dynamic electrocardiographic techniques, Winsor[16] showed sustained release nitroglycerin tablets provided significant protective activity against ischemic S-T depression in patients monitored throughout the day.

Conclusion: It seems to us, who each represent a half century of investigation in the field of nitrite-nitrate therapy, that Needleman's investigations have not nullified in any sense the value of the organic nitrates when taken orally. It is unfortunate that the results of these animal studies should have been made available to the public. Indeed, if Needleman is correct, William Murrell's anginal patients would have failed to benefit by taking nitroglycerin orally, and medicine would have been deprived of this useful drug for the past century, and we and Needleman would not have worked with nitroglycerin.

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LETTERS TO THE EDITOR

ACUTE SUPPURATIVE AMEBIC PERICARDITIS

If the bibliography of Costa et al.[1] included 1972 publications, the authors ignored 11 cases published in 1972[2] as did the reviewing editor of the Journal. Our group[2–4] has described 17 patients, of whom 7 survived, emphasizing that the clinical findings can suggest progressive myocardial compression or cardiac tamponade, with or without sepsis, in patients with or without a diagnosis of amebic abscess of the liver or a past medical history of dysentery and that the pus may not be reddish-brown or resemble anchovy sauce. We believe that the latter points have previously been overstressed and their absence may mislead some clinicians since a high degree of suspicion is required in addition to the use of all available diagnostic tools such as liver scan and serologic tests to confirm the diagnosis. We do not agree that "conservative management" is advisable in the early stage of the lesion, although this statement seems to be in conflict with an earlier statement: "early drainage is advised"; in our more recent cases, including two unreported ones, early subxyphoid drainage[5,6] proved easy and lifesaving and permitted the correct diagnosis or its confirmation.

Amebic abscesses of the liver can open into the pericardium, thus causing the death of a patient who is under proper medical therapy; surgical maneuvers might be needed to prevent this complication.

Finally, a philosophical consideration. Can the authors of a paper ignore a similar publication of a larger series, and the journal receiving the paper ignore such an omission? Should the burden be placed on the authors, or is the reviewer to be blamed when statements as "up to 1972 only 80 cases were reported" and 11 more, published that same year in an international journal are not mentioned?

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REPLY

Our statement recommending conservative management in the early stages of the lesion does not "conflict" with our recommendation for early open pericardial drainage; the two statements are not related. The second one refers to early drainage of the pericardial sac through a tube, as performed in the case reported. If this measure is combined with proper early diagnosis and medical treatment, a good survival rate may be achieved. The statement recommending conservative management refers to classic open chest pericardiectomy in the early stages of constrictive pericarditis, which may develop shortly after the acute phase, as happened in our case: the reported mortality rate for this procedure is very high.

We have now had the opportunity to read the paper of Ibarra-Perez et al., which would have been included in our reference list if we had been aware of it earlier. However, how large a reference list should be is also a matter of philosophy. The main objective of our report was to offer a well documented case of an uncommon condition, emphasizing the following points: (1) the clinical presentation primarily as acute pericarditis with tamponade; (2) the possibility of confusion with the more common acute tuberculous pericarditis; (3) the need for early open pericardial drainage, since signs of severe cardiac compression have a tendency to recur in this condition; (4) the simple way to visualize by X-ray film the liver abscess by injecting contrast material through the tube placed into the pericardial cavity; (5) the need, despite treatment with appropriate doses of chloroquine (Aralen®) and metronidazole (Phlagyl®) for treatment with emetine hydrochloride to achieve complete recovery from the acute phase; and (6) the possibility of early development of constrictive pericarditis. Thus, in light of these objectives, once a certain number of papers giving support to these points were found, the reference list was considered satisfactory.

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SEQUENTIAL STUDIES OF LEFT VENTRICULAR FUNCTION

McAnulty et al.[1] offer a wealth of information, previously unavailable, on the reproducibility (or lack of it) of commonly recorded parameters of ventricular function. Their conclusion that "The range of these day to day changes in the parameters of left ventricular function without therapeutic intervention must be considered when evaluating the effect of therapy" is of interest to physicians and surgeons alike. Furthermore, their finding that "wall motion abnormalities (instead) were constant in site and showed little variation in extent" will be received with enthusiasm by those of us who had insisted on the value, simplicity and

reliability of plain left ventriculography as one of the better tools for the evaluation of left ventricular function in patients with ischemic heart disease.

I have no criticism for a well conducted and extremely useful study by this excellent group of investigators. Furthermore, I would have considered it perfectly proper, for the sake of this investigation, that a number of consenting patients be studied on successive days in order to obtain the two needed sets of information. What disturbs me is a statement indicating that "patients in stable conditions underwent elective diagnostic cardiac catheterization and coronary arteriography *on successive days in two laboratories, the usual practice at this institution.*" (Italics By Dr. Gensini.)

If this is the usual practice in a highly respected institution, such as the University of Oregon Medical School, what next? Should a patient in a less advanced laboratory expect to have his right coronary artery studied on Monday, the left on Tuesday, have angiography on Wednesday and the right and left heart catheterization on Thursday and Friday? Should we take left oblique views only on the odd days and reserve the right oblique views for the even days?

A complete diagnostic study, inclusive of right and left heart catheterization, cardiac output, left ventriculography in two views, coronary arteriography in multiple views, with pressure measurements both before and after stress and vasodilators, can often be accomplished in less than 60 minutes from "skin to skin," using a single cutdown procedure. The simpler combination of left heart catheterization, left ventriculography and coronary arteriography is usually carried out in 30 minutes or less and is considered a standard operating procedure in many laboratories, including our own.

A serious breakdown in administrative policy or unexplainable divisions of responsibility or both must be at work whenever a patient, in order to obtain the same set of information, must be "invaded" twice in two different laboratories.

I am a cardiologist and naturally I believe that the study of the heart is most appropriately performed by a well trained cardiologist. I have nothing against delegating that responsibility to someone primarily trained in another specialty, provided (1) his or her training in invasive cardiovascular techniques is the same as the one that a cardiologist would have to acquire in order to be qualified, *and* (2) there is no other qualified cardiologist willing or able to take on this responsibility. I am, however, profoundly disturbed by "usual practices" such as these and I hope that they will be voluntarily corrected, wherever they may exist.

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Reference

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REPLY

A proper evaluation of the left ventricle should consider its overall systolic function and wall motion in addition to its diastolic properties.[1] A word of caution against visual evaluation of left ventricular function from angiograms is appropriate because such assessments have a significant error rate.[2] For these reasons, several parameters should be measured to evaluate left ventricular function adequately.

At our institution complete hemodynamic evaluation and coronary angiography are often performed on separate days. Many patients undergoing such evaluations do not have coronary artery disease as their primary problem. This approach has allowed us to obtain complete studies without increasing the overall morbidity or mortality. In fact, we wish to emphasize the very low overall complication rate of our studies.[3–9] None of the patients described in our recent study had any complication.

Thromboembolic episodes are the most frequent of the major complications of arterial studies. They are probably related to the length of time the catheter and wires are in the artery, the number of catheter exchanges and the technique used.[10,11] Studies on separate days decrease both the length of time any one catheter is in the arterial system and the number of catheter exchanges in any one study. The required additional arterial puncture for a dual study has not increased morbidity or difficulties with subsequent restudies.

Our practice has allowed us to obtain thorough evaluations of cardiac function and of the coronary arterial system without subjecting patients to an increased risk. When possible, a complete evaluation with one study is preferable. However, in patients needing invasive studies, what is of primary importance is to obtain with consistency complete, reliable and accurate information at low risk.

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LIFE EXPECTANCY AND MARATHON RUNNING

Dr. McIntosh correctly identifies the factors affecting the life expectancy of the American adult by calling for a "change in life styles." [1]

Because of the absence of fatal coronary heart disease among marathon runners,[2] their life style is under study by the American Medical Joggers Association (AMJA). Distance running is being used in rehabilitation centers in Toronto and Honolulu. Several patients have trained up to the 42 km run after recovering from myocardial infarction. Problems in motivation have been partially solved by changing the emphasis from "patient" to "athlete" in the early stages of rehabilitation. Even during the closely supervised walking stages the patient has his eye on the December AMJA Honolulu Marathon. He trains with team-

mates who are at the same level of fitness. Their coach is a cardiologist. AMJA pathologists expect not only a decrease in the incidence of coronary heart disease, but also, because of the teetotaling life style, fewer cases of cirrhosis, carcinoma of the lung, emphysema and generalized arteriosclerosis.

Such programs may give us the increase in life expectancy of which McIntosh speaks.

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REPLY

Intuitively, I believe that a well planned jogging program is important as both a prophylactic and a rehabilitative measure. Yet I believe that the data that prove this hunch correct are not yet available. I hope that the role of exercise in the treatment and prevention of coronary artery disease will be clarified soon.

I hope, too, that Dr. Bassler will not continue to refer to AMJA pathologists who "expect not only a decrease in the incidence of coronary heart disease; but because of the teetotaling life style, they also expect to see fewer cases of cirrhosis, carcinoma of the lung, emphysema and generalized arteriosclerosis." I hope that the pathologic data that become available to the American Medical Joggers Association will be examined by pathologists without preconceived ideas.

Whether or not jogging increases life expectancy and reduces the progression of coronary artery disease, I, for one, can attest to the fact that it improves the quality of life. I do not believe, however, that one has to be a marathon runner to enjoy the benefits of reconditioning or to remain in good physical condition. I cannot emphasize strongly enough that the middle-aged, obese, smoking, sedentary male should not embark on a self-designed exercise program. He should have a careful physical examination with stress testing to be sure that if he does have ischemic heart disease that he is well aware of the limits to which he can exert without developing the process.

Finally, Dr. Bassler's enthusiasm is gratifying and I am sure infectious. I hope that he will always separate intuition from facts and so inform his listeners.

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ACUPUNCTURE ANESTHESIA FOR OPEN HEART SURGERY—I

I read with great interest Dr. Katz's account of acupuncture anesthesia for open heart surgery. I too was a doubting Thomas about the much acclaimed wonders performed by our Chinese colleagues using acupuncture anesthesia in heart surgery until May 1972 when I visited the People's Republic of China and observed several closed mitral commissurotomies performed under acupuncture anesthesia and July 1973 when I returned there to witness several open heart operations performed under acupuncture anesthesia. It was only after I had seen with my own eyes, as Dr. Katz has with his, that I became convinced that indeed it was, is and will be possible to do open heart operations using the technique of total cardiopulmonary bypass under acupuncture anesthesia.

Dr. Katz's account of operative repair of a ventricular septal defect in a youngster under acupuncture anesthesia is identical to what I saw being successfully accomplished in the same hospital and by the same surgical team, many members of which were my former schoolmates and classmates. For documentary purposes, I had the entire operation filmed through the courtesy of the Shanghai Branch of the Chinese Medical Association.

More than 100 open heart operations have been performed under acupuncture anesthesia in that hospital since its first on April 19, 1972, with a success rate of over 90 percent. The types of congenital heart disease so treated included ventricular septal defect, atrial septal defect, pulmonary stenosis, trilogy of Fallot, tetralogy of Fallot and ruptured aortic sinus of Valsalva with ventricular septal defect. The youngest patient was 10 years of age and the longest period of extracorporeal circulation was 121 minutes. My Chinese colleagues neither considered acupuncture anesthesia to be a panacea for all open heart operations nor claimed perfection with this technique. Three "castles" or hurdles still remain in acupuncture anesthesia: incomplete relief of painful sensations during closure of median sternotomy, incomplete muscular relaxation during abdominal operations and uncomfortable sensation during mesenteric traction of gut handling. However, my Chinese colleagues are determined to lick these problems.

Physicians in the western world tend to be somewhat critical of happenings that cannot be explained on a "scientific" basis. In fact, some even called acupuncture anesthesia a form of hypnosis. Such an attitude reflects ignorance and mulishness. I suggest to some of my American colleagues that we keep our mouths closed but our eyes open for further progress and development emanating from the medical horizons in the People's Republic of China.

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ACUPUNCTURE ANESTHESIA—II

Medical journals should publish reports of clinical studies of methods that seem unlikely to be successful by our previous experience; there would be no progress otherwise. But this report of Dr. Katz is, in the language of the courtroom, hearsay evidence. Katz was not the physician in charge; he was not the surgeon; his closest contact to the patient was observation in the operating room. There is no evidence that he examined the patient beyond his observations in the operating theater. I doubt that you would publish a case report submitted by an observer, however interested, whose evidence consisted of the material presented here.

Reuben Berman, MD
Editor
Minnesota Medicine

CARDIAC PACING IN ACUTE MYOCARDIAL INFARCTION

Waters and Mizgala,[1] in their study of the role of cardiac pacing, conclude that "prophylactic temporary transvenous pacemaker insertion in patients with acute myocardial infarction complicated by incomplete bilateral bundle branch block is of little value." It is dangerous to draw such a conclusion from the small number of patients analyzed. As the authors note, the overall mortality for patients with incomplete bilateral bundle branch block in their study is lower than that in other reported series. This discrepancy may be a result of the skilled application of prophylactic and emergency cardiac pacing in this group of patients. Of the group of 15 patients in whom complete heart block developed, 3 of 5 with a prophylactic pacemaker survived, whereas only 3 of 10 with a pacemaker implanted at the time of development of complete heart block survived hospitalization. One might conclude from this that prophylactic, as opposed to after-the-fact pacemaking significantly increases survival of patients in whom complete heart block develops. In addition, although the authors attribute one death to pacemaker manipulation, they document the possible salvage of six lives (three in prophylactic, three in after-the-fact group) by pacemaking. Of course, neither these nor the authors' conclusions are justified, except as hypotheses for further study of this controversial subject.

Waters and Mizgala's view that the potential gain of pacemaking in these patients "may be counterbalanced by the frequent occurrence of serious ventricular arrhythmias" was previously postulated by Godman et al.,[2] but Post and Killip[3] regard their incidence of pacemaker catheter-induced arrhythmias as atypically high. Perhaps because there is a widespread conviction that certain patients benefit from cardiac pacing, studies comparing patients with acute myocardial infarction who undergo cardiac pacing with exactly matched control groups have not appeared. When and if they do, interpretation will be further complicated by various estimates of the risks of cardiac pacing as related to variations in technique and skill.

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3. **Post MR, Killip T:** Application of cardiac pacing to acute myocardial infarction. In, Textbook of Coronary Care (Meltzer LE, Dunning AJ, ed). Philadelphia and Amsterdam, Charles Press and Excerpta Medica, 1972, p 348

REPLY

We agree that our series is small (27 cases), that our conclusions may not constitute the last word on this important subject and that further observations are necessary, as our purpose was to present some evidence for questioning the widespread belief that acute myocardial infarction complicated by incomplete bilateral bundle branch block must be treated with a prophylactic temporary pacemaker and, as suggested by some, eventually with a permanent pacemaker.

Careful examination of the deaths in our series shows that none of the 12 patients who died succumbed for lack of a prophylactic pacemaker; three died of ventricular fibrillation (including one whose death was directly related to catheter manipulation) and the other nine died of causes related to the severity of their coronary artery disease and to the extent of myocardial infarction. Of the patients in whom complete heart block developed in the absence of a prophylactic pacemaker, all survived long enough to have a pacemaker inserted. On the other hand, of the survivors, complete heart block never developed in nine whereas it did in six; of these six, all survived whether or not a prophylactic pacemaker had been inserted. We agree that once complete heart block appears in such patients, a pacemaker is indicated and indeed could be lifesaving. However, no data, ours included, indicate that ultimate survival in these patients is influenced by prophylactic insertion of a pacemaker. Thus, analysis of this group of patients, however small, tends to support the view that acute myocardial infarction complicated by incomplete bilateral bundle branch block points to very extensive myocardial damage and is complicated by a high incidence of ventricular brady- and tachyarrhythmias, congestive heart failure and cardiogenic shock. Survival seems to be unrelated to the use of prophylactic pacing but rather appears to be determined by the degree of myocardial reserve remaining after the acute event and is often accompanied by gradual regression of the conduction disturbances.

All patients in our series were monitored during the acute phase of this illness and 24 hour lead II recordings were obtained. Analysis of these tracings clearly revealed an unusually high incidence of ventricular arrhythmias in all patients, not only in recipients of prophylactic pacemakers. Our reported high incidence of ventricular arrhythmias is therefore unrelated to the possibility of "variation in technique and skill" but rather to increased ventricular irritability, presumably related to the extensive infarction.

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BLIND DEFIBRILLATION

To the editorial on blind defibrillation by Grace et al.[1] I would add: If a first blind defibrillation does not restore the heartbeat, a second one should be performed immediately. This suggestion is based upon the rare possibility that the initial cardiac arrest was due to ventricular tachycardia and the first blind defibrillation (since synchronizing the electrical impulse is not indicated) might have been triggered during the vulnerable period and resulted in ventricular fibrillation. In that case a second blind defibrillation might restore sinus rhythm.

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Reference

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PREDICTIVE VALUE OF ENZYME STUDIES IN MYOCARDIAL INFARCTION

Rose et al.[1] suggest that serum glutamic oxaloacetic transaminase and creatine phosphokinase values above 200 and

2,000 units, respectively, separated patients with myocardial infarction from those without myocardial infarction after coronary artery bypass surgery. We have measured serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, creatine phosphokinase, lactic dehydrogenase, hydroxybutyrate dehydrogenase and the isoenzymes of creatine phosphokinase and lactic dehydrogenase in a variety of clinical settings and have concluded that the laboratory can offer little help in ruling in or ruling out myocardial infarction immediately after coronary artery bypass surgery.

Furthermore, our analysis of the data presented by Rose et al. leads us to a conclusion opposite to the one they present. They fail to recognize that the usefulness of a diagnostic test is related to the prevalence of the disease. Table I shows the results if their data are entered into the model

TABLE I

	Positive Test	Negative Test
Patients with MI (no.)	4	1
Patients without MI (no.)	3	42
Total	7	43

MI = myocardial infarction.

proposed by Vecchio.[2] The sensitivity of their test system was only 80 percent, since only four of five patients with myocardial infarction had a positive test. The specificity of their test was 93 percent since 42 of the 45 patients without infarction had a negative test. The prevalence of myocardial infarction in their series was 10 percent. When a test with a sensitivity of 80 percent and a specificity of 93 percent is applied to a population with a disease prevalence of 10 percent, the predictive value of a positive result is only 57 percent. This means that only 57 percent of the positive results are true positives. There were seven patients with values for serum glutamic oxaloacetic transaminase and creatine phosphokinase above the limits set, but only four of the seven had a myocardial infarction. A 43 percent false positive rate is not acceptable.

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2. **Vecchio TH:** Predictive value of a single diagnostic test in unselected populations. N Engl J Med 274:1171–1173, 1966

REPLY

We agree with Drs. Galin and Gambino that determination of serum enzymes is not an ideal method for detecting myocardial infarction in the patient who has undergone coronary bypass surgery. However, their comments concerning the specificity of positive tests may be open to further interpretation. It is possible that in the circumstances in which the electrocardiogram is used to evaluate whether the patient had an infarction one may underdiagnose the incidence of this complication. Accordingly, the three subjects in our study who exhibited positive enzyme abnormalities but no electrocardiographic changes may have undergone infarction and perhaps the results in these cases should not really be thought of as false positive. Of course, this issue cannot be resolved now. Further analysis of serum enzymes with use of more specific analyses, such as MB creatine phosphokinase, may be of help in this regard. Nevertheless, it may be that with use of a combination of electrocardiographic and enzyme changes the specificity of the two taken together may be enhanced.

A somewhat similar method to that described by Vecchio was developed by Kuipers and Hanssen[1] and applied by van Herpen.[2] This method has an "index of merit" for a contingency table of reality vs. prediction. The index of merit varies from 0, when there is no association between prediction and reality, to 1, if they are completely associated. By using this method and applying it to our data a value of 11/15 is obtained. This indicates a fairly high degree of reliability for the method under question, that is, use of the enzyme abnormalities for the detection of myocardial infarction.

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GRAFT PATENCY AND SERUM TRIGLYCERIDES

Allard et al.[1] recently proposed that graft closure is well correlated with serum triglyceride levels. However, there is no information as to other pertinent factors that may not have been matched in the various groups. For instance, it would have been helpful to know if the flow rates in the grafts measured interoperatively were significantly different in the patients with high and low triglyceride levels; that is, not to assume that triglycerides as such had affected the graft flow but that the difference in graft flow may have also been a factor in graft closure. One can think of several factors that should have been matched and must be wary of accepting results when the patient population being evaluated acts as its own control. The presumptive conclusion of the authors is one worth pursuing in a further matched study.

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Reference

1. **Allard C, Goulet C, Grondin CM, et al:** Patency of aortocoronary vein grafts and serum triglycerides. Three year follow-up study. Am J Cardiol 33:679–680, 1974

REPLY

We entirely subscribe to the suggestion that the patency of aortocoronary vein grafts was influenced by the concentration of serum triglycerides. The study of serum triglycerides and vein graft patency should be pursued with matched controls. Such an investigation is now being car-

ried out in a prospective study of about 400 randomly selected patients. In our first study of this relation,[1] 70 patients (99 grafts) were investigated, taking into account the state of the segments distal to the grafts; the degree of atherosclerosis and the vascular bed were chosen as criteria for defining a good runoff.[2] In the patients with good runoff the serum triglyceride concentration was greater in the group with occluded grafts than in the group with patent grafts 1 year after operation. Since occlusion is uncommon between 1 and 3 years after operation and little or no reduction occurs in the diameter of the graft,[3] it seemed a fruitless effort to correlate again the triglyceridemia and the graft flow, inasmuch as the number of patients was small.

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BOOK REVIEWS

THE NORMAL APEXCARDIOGRAM, by Jos. L. Willems. Brussels, Arscia Uitgaven N. V., 1973, 305 pages

This monograph represents a detailed analysis of the normal apexcardiogram together with systolic time intervals as obtained by standard methods. There are three sections to the monograph: (1) methods and background information; (2) apex cardiography and noninvasive timing of intracardiac events, which is primarily concerned with systolic time intervals; and (3) apex cardiography as a noninvasive assessment of cardiac function.

The data were obtained from a large series of normal subjects. Extensive measurements of the apex cardiogram were performed as well as statistical analysis, which produced a voluminous number of tables. The section on myocardial contractility is probably a step forward in the use of noninvasive techniques for assessment of this variable, but many criticisms can be made of this section. To some extent it seems superficial, and assumptions are made for which there are no means of validation. Studies performed in dogs are emphasized throughout the monograph although, because of the differences in anatomy and the fact that the dog essentially has no mediastinum, the dog is probably a poor model for studying movements of the human heart as reflected on the chest wall. It was surprising that the results were as consistent as they were. Although a fair amount of emphasis is placed on computer technology, it is poorly explained and it is not clear whether computer techniques were used in obtaining all the measurements presented in the various tables. An index is not provided.

The book is a reference manual only for normal data and would be of interest only to investigators working in the field. It should be pointed out that much of the data will be of little importance unless the studies are extended to include patients with heart disease.

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THE MAMMALIAN MYOCARDIUM, edited by Glenn A. Langer and Allen J. Brady. New York, John Wiley, 1974, 310 pages, $24.50

The formulation of a comprehensive text on the rapidly expanding and complex subject of the subcellular function of the myocardium is a most ambitious and difficult undertaking. Yet, application of the well recognized expertise of the editors has resulted in the synthesis of a smoothly organized and delightfully readable monograph that provides an authoritative perspective on the present state of knowledge and important insight concerning unsolved problems. The book is composed of 10 integrated chapters by outstanding investigators: (1) myocardial ultrastructure (McNutt and Fawcett); (2) contractile proteins (Katz); (3) active transport in mammalian myocardium (Schwartz); (4) cardiac energetics (Gibbs); (5) electrophysiology of cardiac muscle (Brady); (6) mechanics of the myocardium (Brady); (7) ionic movements and control of contraction (Langer); (8) adrenergic mechanisms (Rolett); (9) coronary circulation (Berne); and (10) myocardial cell failure (Fanburg).

This monograph should serve as an excellent beginning reference for a diverse group of students, including graduate students in the medical sciences, physicians-in-training and academic cardiologists. It is excellent, too, for practicing specialists and generalists who desire to improve their understanding of recent advances in the fundamental mechanisms governing cardiac performance.

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REVIEWS IN CARDIOLOGY*

A Cooperative Program of the American College of Cardiology and the National Library of Medicine

ADRENAL GLAND NEOPLASMS

Familial tumor endocrinopathies. Schimke RN. **Birth Defects 7(6):55-65, May 71 (64 ref.)**

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Left ventricular function and myocardial contractility: analysis by roentgen videoangiographic techniques. Ritman EL. **Mayo Clin Proc 50(3):147-56, Mar 75 (61 ref.)**

ARRHYTHMIA

Electrophysiology and pharmacology of cardiac arrhythmias. VI. Cardiac effects of verapamil. Rosen MR, et al. **Am Heart J 89(5):665-73, May 75 (45 ref.)**

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Macromolecules in the arterial wall in relation to injury and repair--a survey. Berenson GS, et al. **Angiology 25(10):649-81, Nov 74 (33 ref.)**

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Disorders of the autonomic nervous system. Chapter 4. Disorders of cardiac control. Johnson RH, et al. **Contemp Neurol Ser (11):59-66, 1974 (35 ref.)**

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Disorders of the autonomic nervous system. Chapter 3. The nervous control of the circulation and its investigation. Johnson RH, et al. **Contemp Neurol Ser (11):33-58, 1974 (109 ref.)**

Disorders of the autonomic nervous system. Chapter 7. Some disorders of regional circulation. Johnson RH, et al. **Contemp Neurol Ser (11):114-28, 1974 (85 ref.)**

BLOOD CIRCULATION

Disorders of the autonomic nervous system. Chapter 3. The nervous control of the circulation and its investigation. Johnson RH, et al. **Contemp Neurol Ser (11):33-58, 1974 (109 ref.)**

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BLOOD FLOW VELOCITY

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HEART

Ultrasound in the diagnosis of congenital heart disease. Murphy KF, et al. **Am Heart J 89(5):638-56, May 75 (99 ref.)**

Disorders of the autonomic nervous system. Chapter 4. Disorders of cardiac control. Johnson RH, et al. **Contemp Neurol Ser (11):59-66, 1974 (35 ref.)**

HEART CONDUCTION SYSTEM

Electrophysiology and pharmacology of cardiac arrhythmias. VI. Cardiac effects of verapamil. Rosen MR, et al. **Am Heart J 89(5):665-73, May 75 (45 ref.)**

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Ultrasound in the diagnosis of congenital heart disease. Murphy KF, et al. **Am Heart J 89(5):638-56, May 75 (99 ref.)**

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Current application of echocardiography. Abbasi AS. **Angiology 26(4):303-16, Apr 75 (27 ref.)**

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Intra-axonal transport of neurotransmitters in mammalian neurons. Dahlström A, et al. **Symp Soc Exp Biol** (28):229-47, 1974 (97 ref.)

PHEOCHROMOCYTOMA

Multiple mucosal neuromas, pheochromocytoma, medullary carcinoma of the thyroid and marfanoid body build with muscle wasting: reexamination of a syndrome of neural crest malmigration. Gorlin RJ, et al. **Birth Defects** 7(6):69-72, May 71 (43 ref.)

Phaeochromocytoma. Wolf RL. **Clin Endocrinol Metabol** 3(3):609-21, Nov 74 (115 ref.)

PULMONARY HEART DISEASE

Cor pulmonale (pulmonary heart disease): present-day status. Ferrer MI. **Am Heart J** 89(5):657-64, May 75 (66 ref.)

THROMBOEMBOLISM

Thromboembolic disorders in pregnancy: pathophysiology, diagnosis, and treatment, with emphasis on heparin. Flessa HC, et al. **Clin Obstet Gynecol** 17(4):195-235, Dec 74 (153 ref.)

THROMBOPHLEBITIS

Treatment of thrombosis of veins of the lower extremities. Adar R, et al. **N Engl J Med** 292(7):348-50, 13 Feb 75 (40 ref.)

Platelet inhibition in the management of thrombosis. Didisheim P, et al. **Thromb Diath Haemorrh** 32(1):21-34, 30 Sep 74 (67 ref.)

Diagnosis of thrombosis. Evaluation of 125I-fibrinogen scanning and blood tests. Hirsh J, et al. **Thromb Diath Haemorrh** 32(1):11-20, 30 Sep 74 (55 ref.)

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Degradation products of fibrinogen and crosslinked fibrin-projected clinical applications. Marder VJ, et al. **Thromb Diath Haemorrh** 32(1):49-56, 30 Sep 74 (35 ref.)

VASCULAR DISEASES

Injury and repair in arterial tissue: experimental models: types and relevance to human vascular diseases--a survey. Björkerud S. **Angiology** 25(10):636-48, Nov 74 (34 ref.)

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VASODILATOR AGENTS

Renal vascular tone in essential and secondary hypertension: hemodynamic and angiographic responses to vasodilators. Hollenberg NK, et al. **Medicine (Baltimore)** 54(1):29-44, Jan 75 (71 ref.)

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Borys Surawicz, MD, FACC, Chairman
National Program Committee

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1975

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

OCT. 6–15 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. University of Missouri—Kansas City School of Medicine, Kansas City, Mo.

OCT. 8–9 — **Louis N. Katz Symposium—Coronary Artery Disease 1975: Dilemma, Dialogue and Decision.** Sylvan Weinberg, FACC, Leonard S. Dreifus, FACC, Herman Hellerstein, FACC, directors and Homer D. Cassel, FACC, honorary program director. Good Samaritan Hospital, Dayton, Ohio

OCT. 9–11 — **New Techniques and Concepts in Cardiology: Pathogenesis, Diagnosis and Treatment of Coronary Atherosclerosis.** Stephen E. Epstein, FACC, director. Washington Hilton Hotel, Washington, D.C.

OCT. 14–16 — **Ischemic Heart Disease: Current Concepts.** William J. Grace, FACC, director and Richard J. Kennedy, FACC and James T. Mazzara, FACC, co-directors. St. Vincent's Hospital and Medical Center of New York, New York, N.Y.

NOV. 6–8 — **Core Curriculum: Phonocardiography and Pulse Recording—Workshop.** Morton E. Tavel, FACC, director. The Methodist Hospital Graduate Medical Center, Indianapolis, Ind.

NOV. 12–14 — **Core Curriculum: Echocardiography, Phonocardiography and Pulse Tracings—A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

DEC. 7–9 — **Advances in Heart Disease 1976.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, Calif.

DEC. 7–10 — **Structure—Function Correlations in Cardiovascular Disease.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, Va.

DEC. 10 — **Colloquia in Cardiology—Number 8: Stress and the Heart: The Influence and Management of Stress in Heart Disease.** Robert W. Oblath, FACC and Ronald Danzig, FACC, directors. Ambassador Hotel, Los Angeles, Calif.

DEC. 12–14 — **The Dwight E. Harken Symposium: Advances in the Prophylaxis and Therapy of Cardiovascular Disease.** Henry I. Russek, FACC, director. Americana Hotel, New York, N.Y.

1976

JAN. 11–13 — **Future Directions in the Management of Cardiac Disease: A Bicentennial Viewpoint.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC and James S. Forrester, co-directors. Snowmass-at-Aspen, Aspen, Colo.

JAN. 19–22 — **Core Curriculum: Pediatric Echocardiography.** Richard A. Meyer, director and Samuel Kaplan, FACC, co-director. Children's Hospital, Cincinnati, Ohio

FEB. 23–26 — **Twenty-fifth Annual Scientific Session.** Charles Fisch, FACC, president. Marriott Motor Hotel, New Orleans, La.

MAR. 11–13 — **Cardiovascular Disease—1976: Practical Diagnosis and Management.** John Ross, Jr., FACC, Robert A. O'Rourke, FACC, Joel S. Karliner, FACC and Kirk L. Peterson, FACC, directors. La Costa Resort Hotel and Spa, San Diego, Calif.

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- Cite in numerical order every reference, figure and table. (Order of mention in text determines the number given to each.)
- Place acknowledgments at end of text, before references.

THE REFERENCES

- Type in duplicate; double-space.
- Number the references in order in which they are mentioned in text.
- Provide concluding page numbers for all journal references and specific page numbers for all book references. Indicate all abstracts by the abbreviation (abstr).
- Follow the general arrangement, abbreviations and punctuation styles shown below.

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- Identify at the end of each legend and in alphabetical order all abbreviations in the figure described.

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- Give each table a number (in roman numerals; Table I, II, etc.) and a title. Number the tables in order in which they are mentioned in the text.
- Provide a footnote to each table—identifying **in alphabetical order** all abbreviations used.

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For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

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36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

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If your angina patient* isn't having 3 out of 4 better days than usual... try Cardilate®

(ERYTHRITYL TETRANITRATE)

*Please note: unstable angina patients may be refractory to all long-acting nitrates.

INDICATIONS: For the prophylaxis and long-term treatment of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris, rather than for the treatment of the acute attack of angina pectoris, since its onset of action is somewhat slower than that of nitroglycerin.

PRECAUTIONS: As with other effective nitrates, some fall in blood pressure may occur with large doses.

Caution should be observed in administering the drug in patients with a history of recent cerebral hemorrhage, because of the vasodilatation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

SIDE EFFECTS: No serious side effects have been reported. In sublingual therapy a tingling sensation (like that of nitroglycerin) may sometimes be noted at the point of tablet contact with the mucous membrane. If objectionable, this may be mitigated by placing the tablet in the buccal pouch. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics.

Mild gastrointestinal disturbances occur occasionally with larger doses and may be controlled by reducing the dose temporarily.

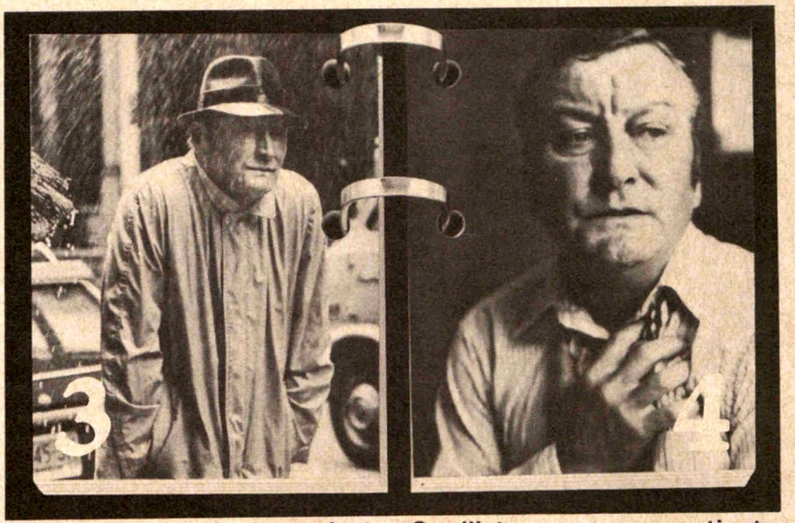
SUPPLIED: 10 mg chewable tablets, bottle of 100. Also 5, 10 and 15 mg scored tablets in bottles of 100. 10 mg scored tablets also supplied in bottle of 1,000.

Also available: Cardilate® P brand Erythrityl Tetranitrate with Phenobarbital* (*Warning: may be habit-forming).

1. Russek HI: AM J M Sc 239:478, 1960

"Pain days" significantly reduced with Cardilate® (erythrityl tetranitrate) in 48-patient study.[1] Patients on placebo experienced same pain as usual or increased pain 2 days out of 3...compared to 1 day out of 4 while on Cardilate.

Rapid-acting chewable tablets (10mg) preferred by many patients. Should be given before anticipated periods of stress to produce an action within 5 minutes and lasting up to 2 hours. Sublingual tablets also available.



Effective prophylaxis against attacks; increases exercise tolerance. Serious side effects have not been reported in 20 years' clinical use.

Cardilate can save patients money; is less expensive than many popular long-acting nitrates. 20% to 30% savings not uncommon...also helps reduce need for nitroglycerin.

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BOOST the efficiency of your staff

New 3rd Edition! **COMPREHENSIVE CARDIAC CARE, A Text for Nurses and Other Health Professionals.** *By Kathleen G. Andreoli, R.N., B.S.N., M.S.N.; Virginia K. Hunn, R.N., B.S.N.; Douglas P. Zipes, M.D.; and Andrew G. Wallace, M.D.* Emphasizing fundamental principles, this leading book discusses coronary artery disease and complications; physical examinations; management of patients with pace-makers; and more. October, 1975. Approx. 288 pp., 959 illus. **About $7.25.**

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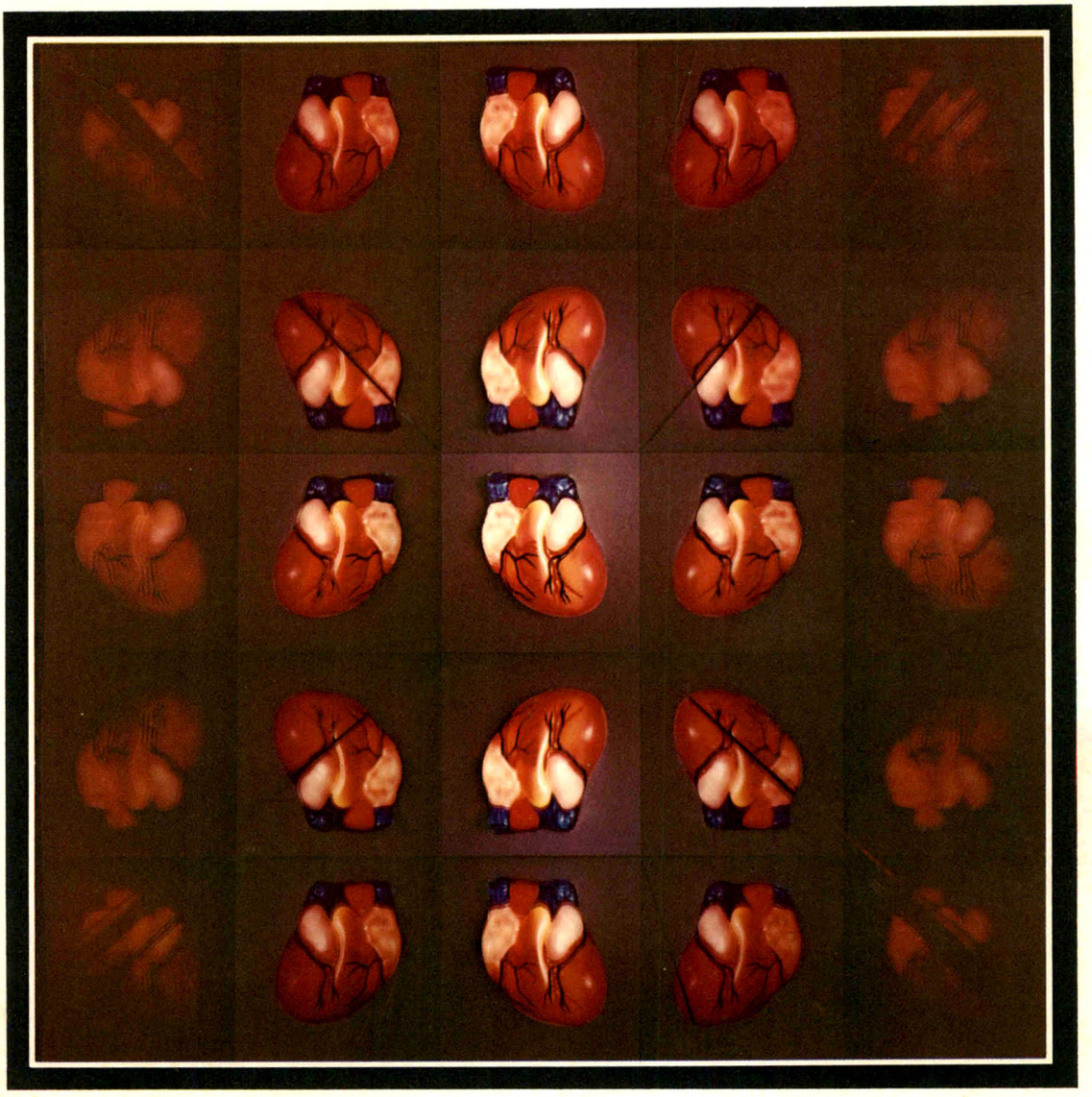
In the shock syndrome due to myocardial infarction



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The drug for the heart that reflects itself in the kidney

INTROPIN®
(dopamine HCl)

Intropin® (dopamine HCl) provides a positive approach in the correction of hemodynamic imbalances in the shock syndrome due to myocardial infarction. Intropin is a drug to consider after you have established an adequate airway and corrected existing hypovolemia.

Intropin is a unique catecholamine that does what you want it to do – increase cardiac output, increase vital organ perfusion and increase urine output without increasing the likelihood of serious undesirable effects.

A key to increased survival of the shock episode is to initiate Intropin therapy as soon as practical after the onset of signs, since the patients most likely to respond are those whose myocardial function, urine output and blood pressure have not undergone profound deterioration. The less time between onset of signs and the initiation of shock therapy, the better the prognosis.

Intropin must be diluted in a suitable intravenous solution and given by I. V. drip.

Increase vital organ perfusion and urine output

Intropin provides increased vital organ perfusion and can significantly increase urine flow in the low-to-moderate dosage range. Increased urine output (plus accompanying sodium excretion) is caused by an increase in the renal blood flow and glomerular filtration.

In contrast, other catecholamines do not consistently increase (and often decrease) urine output.

Intropin may also increase urine output in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation.

When high doses (above 30 mcg/kg/min) of Intropin are administered, urine flow may decrease, and a dosage reduction may be necessary.

Increase in cardiac output, stroke volume and contractility

Intropin substantially increases contractility, stroke volume and cardiac output by acting on the beta receptors of the heart.

The myocardial oxygen supply/demand ratio appears to remain stable with Intropin at low to intermediate doses. Intropin produces less increase in myocardial oxygen consumption than isoproterenol.

Increase blood pressure

Low-to-moderate doses of Intropin are usually sufficient to manage hypotension due to inadequate cardiac output. At these doses, Intropin does not typically increase total peripheral vascular resistance. Blood flow to the mesenteric area may increase while circulation in the peripheral vascular beds may decrease.

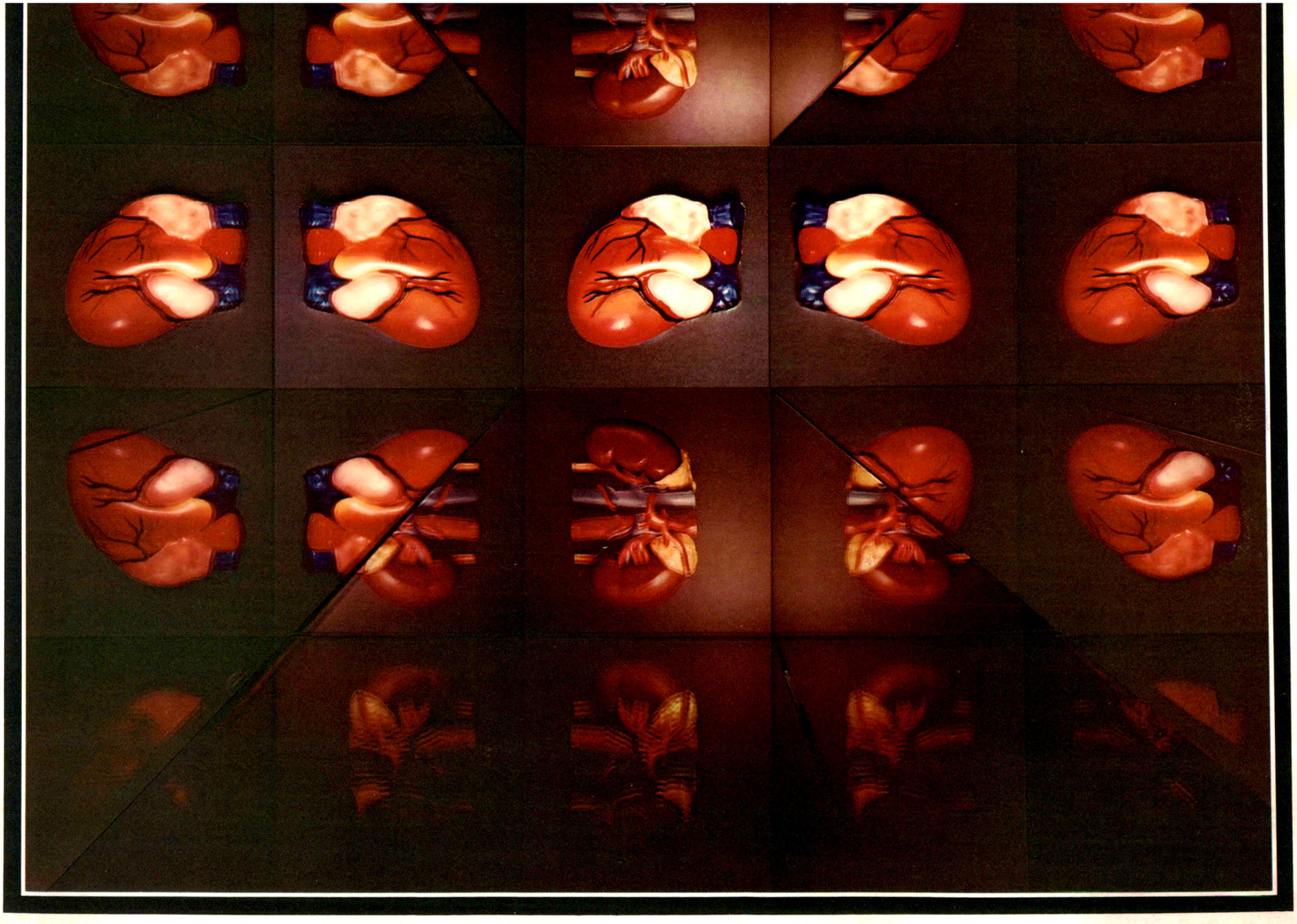
Before administering Intropin, the physician should be familiar with the effects of the drug at various dose levels (see chart). Note especially the paradoxical results of Intropin at the higher ranges (over 30 mcg/kg/min) – increased systemic vascular resistance plus a decrease in renal blood flow and urine output. These phenomena can be reversed, if desired, by reducing the dose.

Increase dosage control

Intropin has a half life of approximately 1.75 minutes, and the positive effects of the drug usually dissipate within 10 minutes after discontinuing the medication.

As shown in the chart, the positive effects of Intropin vary with the dose levels administered. Before using the drug, physicians are advised to familiarize themselves with the Intropin dose phenomena – particularly as they relate to the kidney.

See last page of this advertisement for full prescribing information.



The effects of Intropin® (dopamine HCl) at low, intermediate and high dose levels

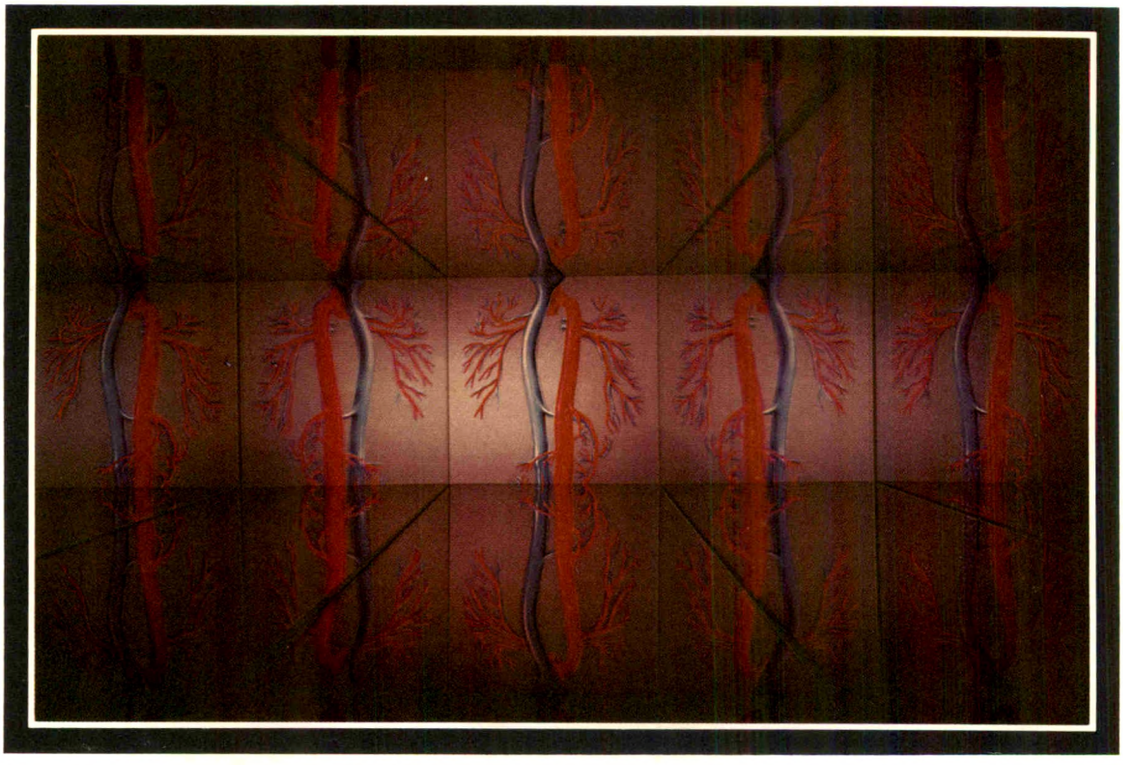
	Low Dose 2-5 mcg/kg/min	Intermediate Dose 5-30 mcg/kg/min	High Dose over 30 mcg/kg/min
Cardiac Output	no change	increase	increase
Stroke Volume	no change	increase	increase
Heart Rate	no change	there is an initial increase followed by a decrease toward normal rate as infusion continues	
Myocardial Contractility	no change	increase	increase
*Potential for Excessive Myocardial Oxygen Demands	low coronary blood flow increased	low coronary blood flow increased	data unavailable
*Potential for Tachyarrhythmias	low	low	moderate
Total Systemic Vascular Resistance	slight decrease to no change	no change to slight increase	increase
Renal Blood Flow	increase	increase	decrease
Urine Output	increase	increase	decrease

Intropin educational materials available

Useful Intropin educational materials (including dosage converters; training kits for critical care personnel; a 20-minute instructional film with accompanying literature; and published clinical reprints) may be obtained through your Arnar-Stone representative, or by contacting Arnar-Stone Laboratories, Inc., directly.

See last page of this advertisement for full prescribing information.

*Low but needs monitoring



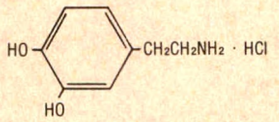
ARNAR-STONE LABORATORIES, INC.
601 E. Kensington Rd.
Mt. Prospect, Illinois 60056

Printed in U.S.A./ASL-08-75-932

INTROPIN® (dopamine HCl)

5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3,4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs—Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output—Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension—Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy—Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children—The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia—Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure—If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation—INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease—Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT—Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics—Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required—Close monitoring of the following indices—urine flow, cardiac output and blood pressure—during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution—Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration—INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.
2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

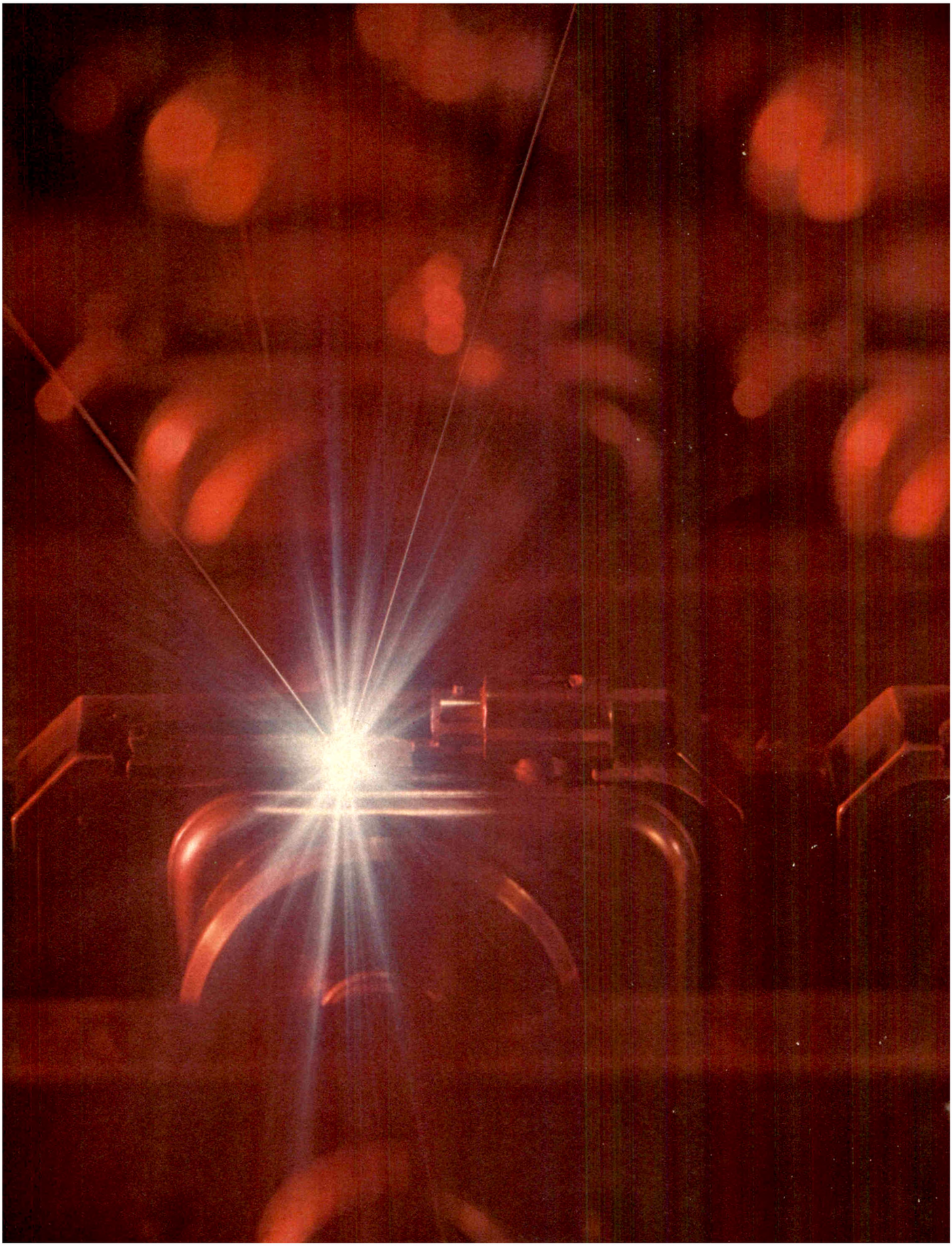
In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.
4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter.

ARNAR-STONE LABORATORIES, INC.
Mount Prospect, Illinois 60056
A Subsidiary of American Hospital Supply Corporation



Sheathed in metal, sealed with an electron beam, the Edwards Model 8116 Pacemaker is designed for survival in the hostile environment of the human body.

Body fluids create a hostile environment for sensitive electronic circuits. It takes only a few sodium ions, seeping through microscopic pores, to jeopardize the integrity of a pacemaker's internal electronics.

Five years of research have now resulted in an improved type of pacemaker package specifically designed to minimize the danger of infiltration by body fluids. The Edwards Laboratories' Model 8116 Ventricular Inhibited Pulse Generator is totally enclosed in a metal container and hermetically sealed with an electron beam.

Safety, the major consideration. The Model 8116 exterior case is fabricated from Haynes Alloy 25, a biologically compatible material. The metal enclosure, encasing both electronics and power supply, also provides extra protection against electromagnetic interference, and results in a reduced profile.

But the ultimate question is the safety and integrity of the exterior seals. Every Model 8116 Pacemaker undergoes two separate evaluation checks, once to test the glass-to-metal electrical seal of the connector, and again to test the electron-beam bond that seals the metal enclosure.

Protection in depth. Additional safety factors include a chemical system for entrapping hydrogen gas (liberated during battery discharge), the strength of the metal enclosure itself, and the electronic filters and metallic shields that protect against electromagnetic interference.

Further reliability and safety are provided by an improved type of battery, the RM-1 Group II Mallory Mercury Cell. Stable timing circuits give advanced warning when batteries near the end of their useful life. Reflecting these improvements, the Model 8116 Pacemaker carries a 48-month warranty and replacement allowance.

For a demonstration of the Model 8116, as an integral part of the complete Edwards Cardiac Pacemaker System, contact Edwards Laboratories, P.O. Box 11150, Santa Ana, California 92711, 714/557-8910, Cable: EDSLAB, Telex: 68:5567.

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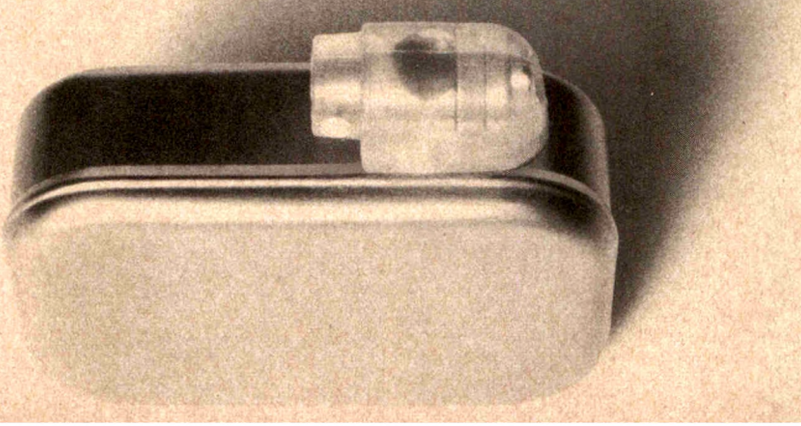
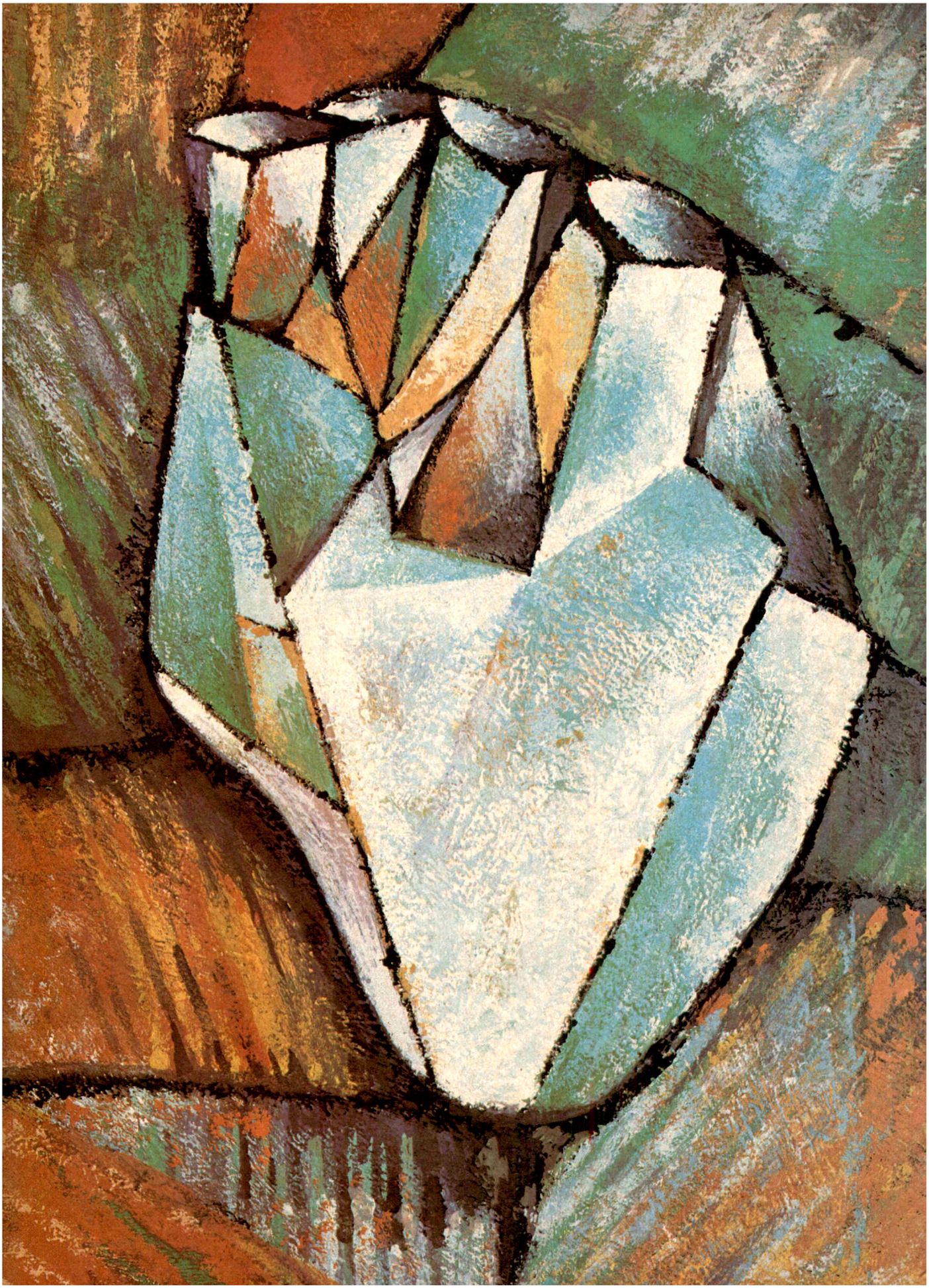
A pacemaker is only as good as its bond.





The art of antianginal therapy

For centuries, treating the heart's ills has been the subtlest of arts. Even today, evaluating a drug for chronic angina pectoris involves the art of medicine as well as its science.

During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Give enough, long enough—The recommended dosage: 50 mg t.i.d. at least one hour before meals for several weeks or longer.

Persantine® Tablets of 25 mg
dipyridamole

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

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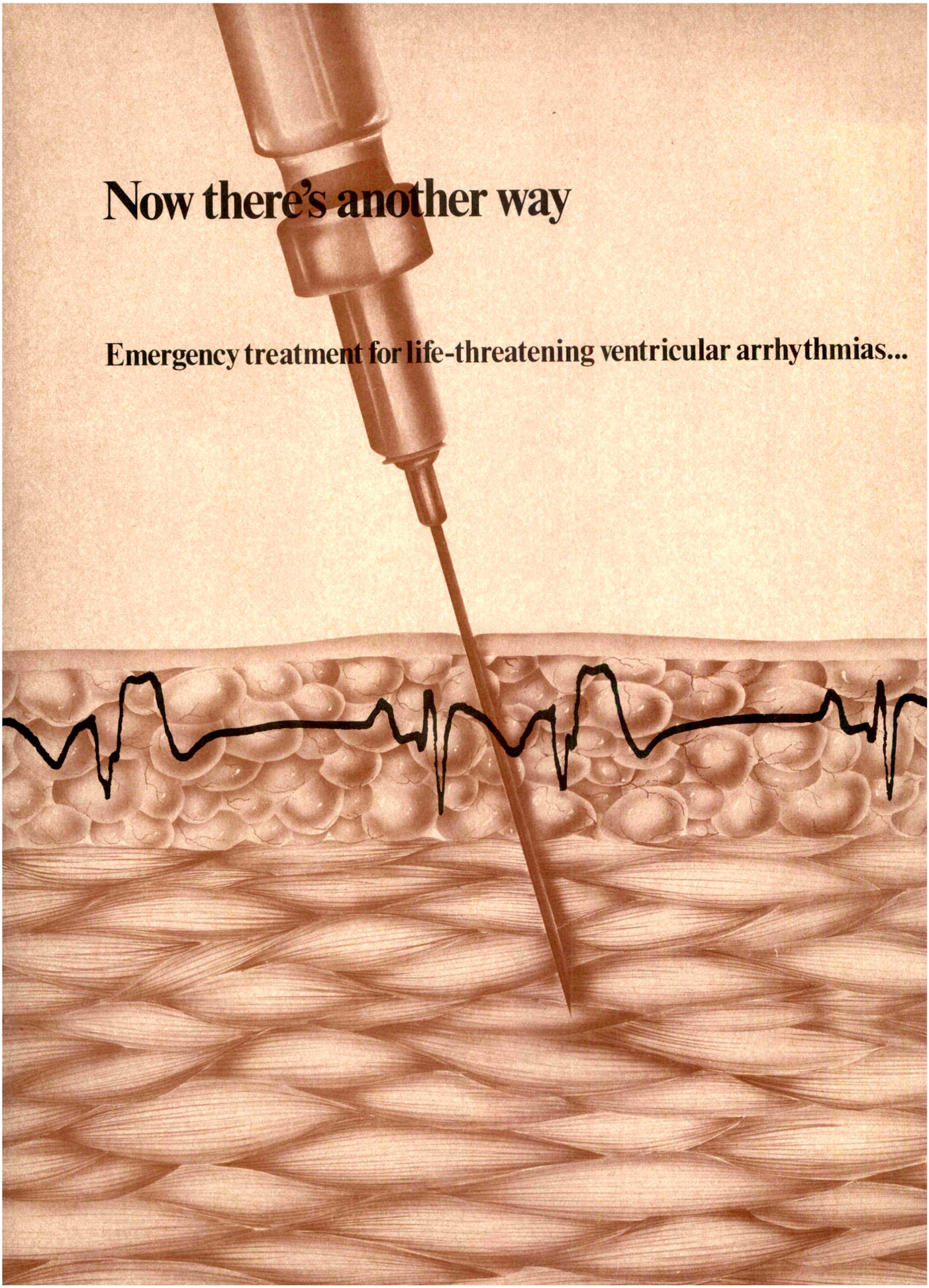
Elmsford, N.Y. 10523

One of a series of paintings of the heart in the style of well-known artists.

The Heart... in the style of Georges Braque (1882-1963)

He and Picasso are considered the originators of cubism, which may be viewed as the classical form of expression for a chaotic world. Braque liked best to paint still life.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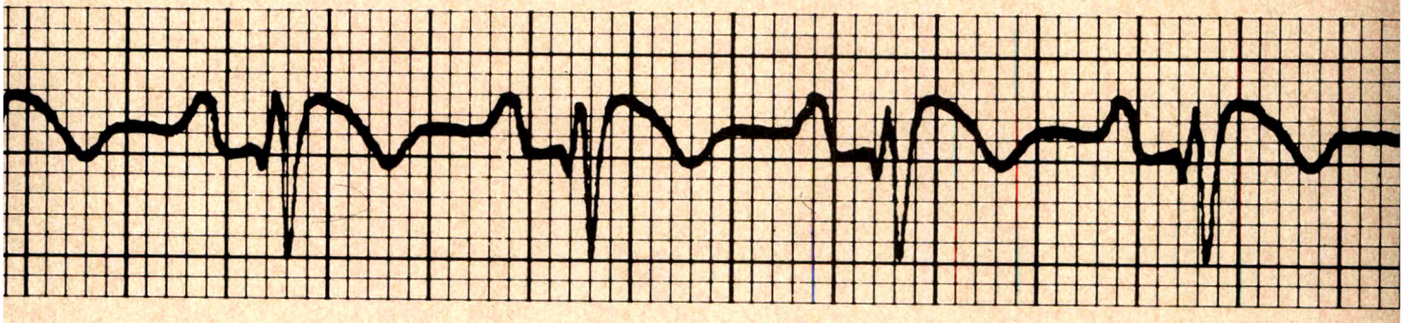
When an appropriate dose of Xylocaine is administered by the intramuscular (deltoid) route, effective antiarrhythmic blood levels are usually attained within 5-15 minutes and may persist for 60-90 minutes. Xylocaine Intramuscular is specifically indicated in the acute management of life-threatening ventricular arrhythmias when justified:

- by a physician when ECG equipment is not available to verify diagnosis, but potential benefits may outweigh possible risks
- by a physician when IV facilities are not available
- by paramedical personnel in a mobile coronary care unit directed by a physician viewing a transmitted ECG

New Xylocaine® (lidocaine) HCl

Intramuscular injection for cardiac arrhythmias

Usual dosage: For the average 150 lb man, 3 ml (300 mg) injected in deltoid muscle. See complete instructions in package insert.



Before prescribing or administering, please consult complete product information, a summary of which follows:

Contraindications: Patients with known hypersensitivity to local anesthetics of the amide type, and patients with Adams-Stokes syndrome or severe degrees of sinoatrial, atrioventricular or intraventricular block.

Warnings: ASPIRATE FREQUENTLY TO AVOID INADVERTENT INTRAVASCULAR ADMINISTRATION.

ECG monitoring is recommended. However, in emergency situations when a physician suspects ventricular arrhythmia and ECG equipment is not available, a single dose may be administered when the physician determines potential benefits outweigh possible risks. If possible, have emergency resuscitative drugs and equipment immediately available to manage potential adverse reactions involving cardiovascular, respiratory, or central nervous systems.

Intramuscular use of Xylocaine® may result in increased creatine phosphokinase levels and compromise the use of this enzyme determination, without isoenzyme separation, in diagnosing acute myocardial infarction.

Pediatric use is not recommended.

Precautions: Observe usual precautions in the presence of impaired renal or hepatic function, hypovolemia and shock, and all forms of heart block.

Adverse Reactions: Although serious adverse reactions to Intramuscular Xylocaine have been rare, the following previously have been reported following lidocaine administration:

1. Central Nervous System—lightheadedness; drowsiness; dizziness; apprehension; euphoria; tinnitus; blurred or double vision; vomiting; sensations of heat, cold, or numbness; twitching; convulsions; unconsciousness; respiratory depression and arrest.
2. Cardiovascular System—hypotension; cardiovascular collapse; bradycardia which may lead to cardiac arrest.

Cross-sensitivity with procainamide or quinidine has not been reported.

Soreness at injection site, occasionally.

Supplied in 5 ml ampules, in cartons of 10. Each ml contains 100 mg of Xylocaine HCl and sodium hydroxide to adjust pH. A 3 ml injection provides the recommended dose.

FOR INTRAMUSCULAR USE ONLY.

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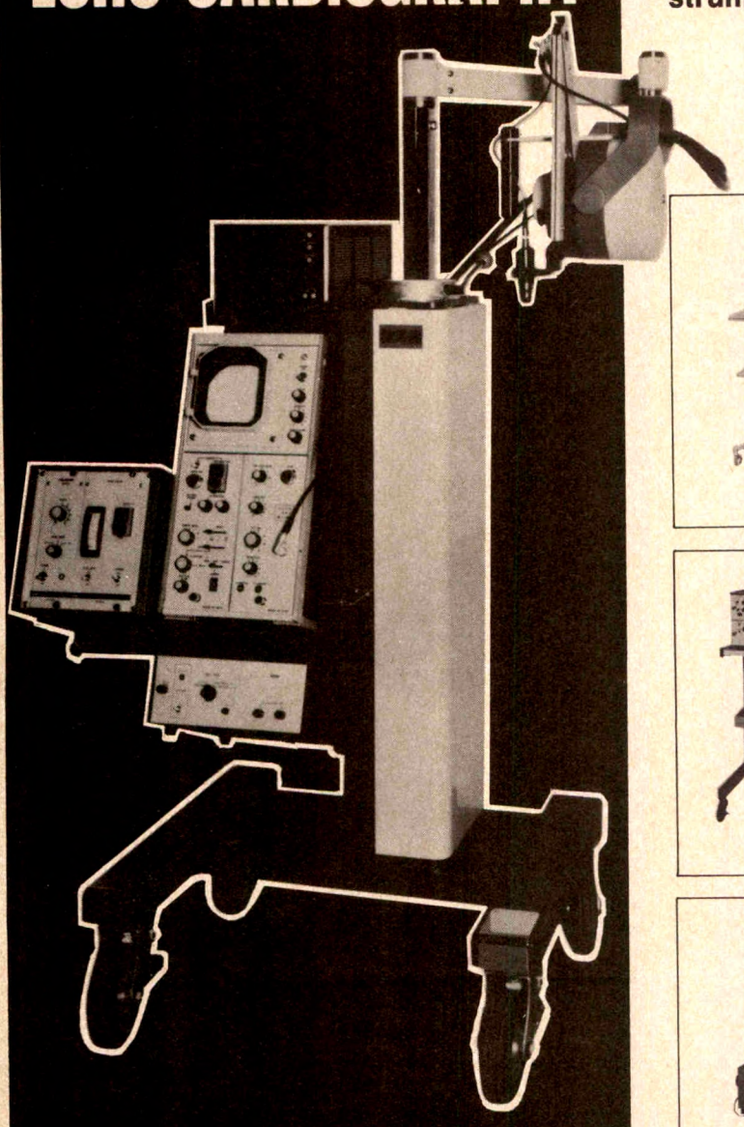

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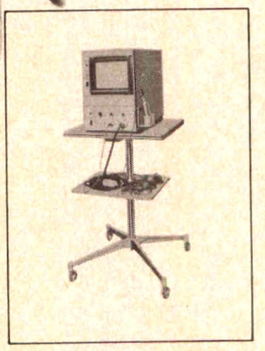
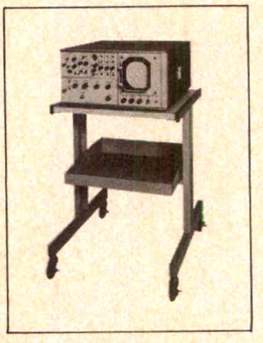
Two dimensional, stop-action image of a heart section formed by a composite of multiple B-Scan recordings at user-selected point in QRS complex.



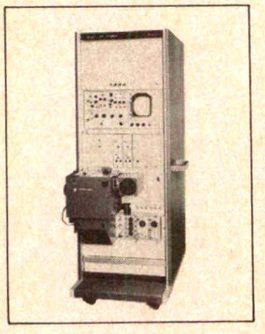
SSD-110 ECHOCARDIOGRAPH

Split screen display of ultrasonic cardiogram in M-Mode and ECG waveform.



SSD-80 ULTRASONIC CARDIOGRAPH

Split screen or full screen overlapping display of ultrasonic cardiogram in M-Mode, plus four (4) additional channels for the biological signals synchronized to the R-Wave.



SSD-90 UCG POLYGRAPH

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For further information contact T. C. Cannon

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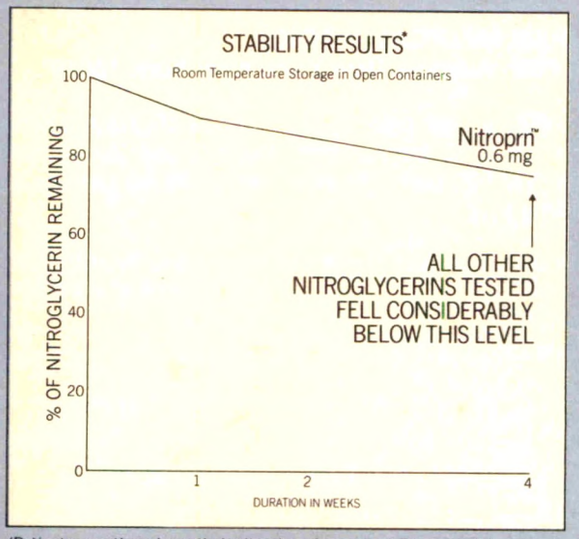

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*Methods used: The semi-automated Content Uniformity Assay based on the procedure of Fusari, S.: J. Pharm. Sci. 62:122 (1973), with modifications by the Applied Analytical Research Laboratories of Warner-Lambert Company. Data

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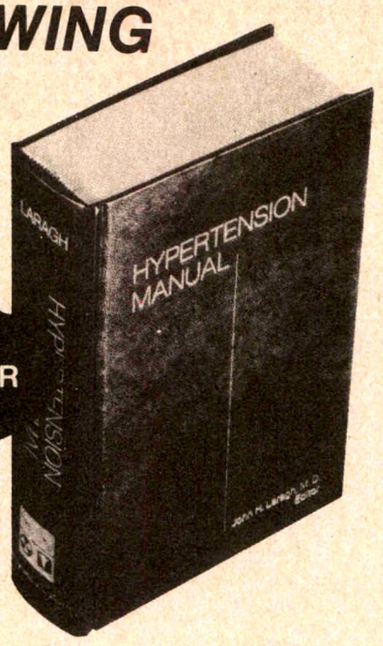

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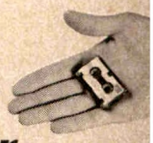

Smaller, lighter compact one-piece unit weighs 25 ounces.

The Remler patented Ambulatory Blood Pressure Recorde has been in use for more than ten years by leading physicians an research institutions throughout the world.

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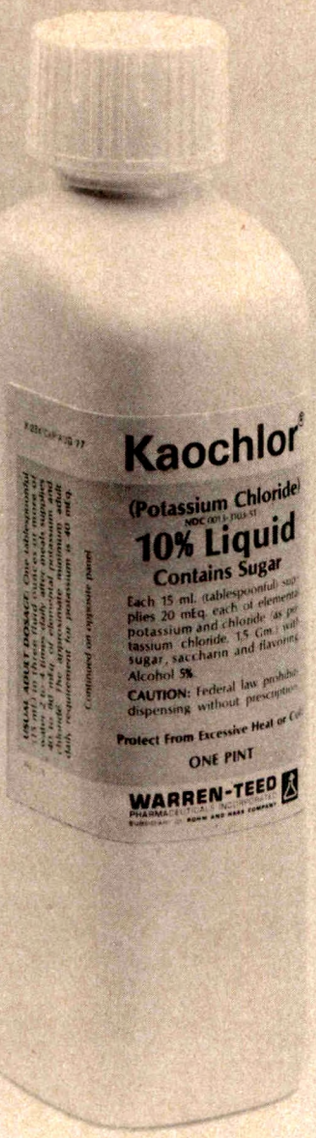

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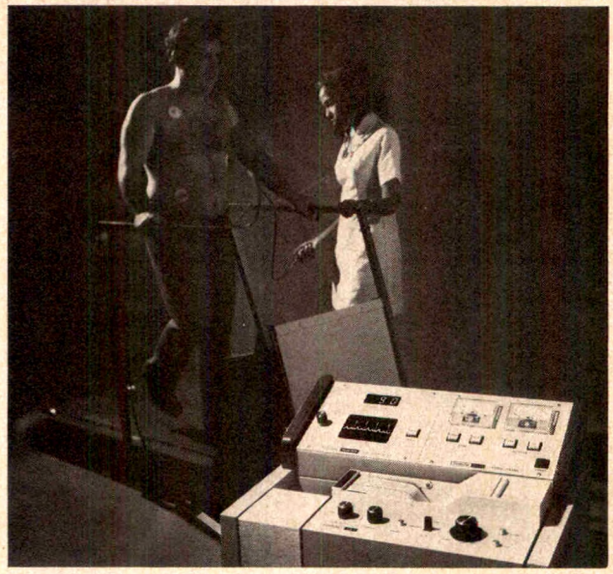

A new, easy-to-operate exercise electrocardiography system designed to stress the patient without straining the physician or the budget.

Cambridge STS is an integrated, easy-to-use system intended for hospital, health care, and athletic facilities, as well as for the practitioner with a limited budget. STS reliably produces exercise test results of excellent quality. It is designed to function superbly as a multistage exercise test system in office or hospital, as a standard, mobile electrocardiograph, or as a rate meter/monitor in the ER, ICU, or CCU.

- Strip chart recorder, ECG monitor, heart rate meter, and optional treadmill meters and controls all located in single mobile console where entire test protocol is controlled, monitored, and recorded.
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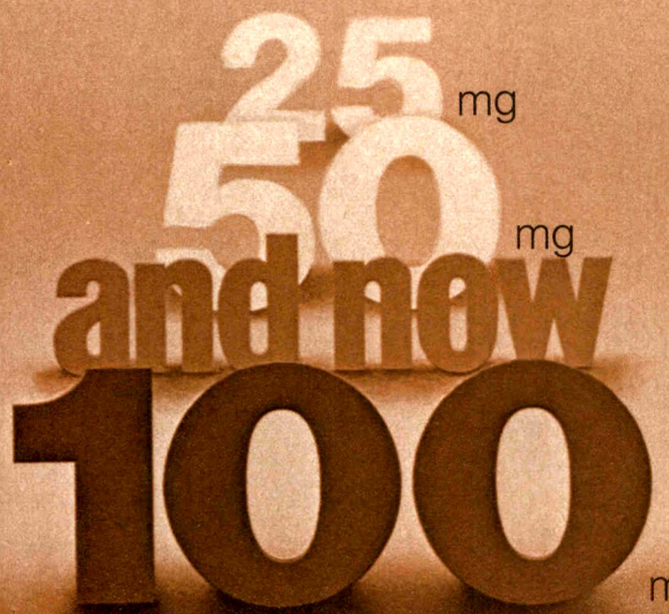

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American offers you a complete line of ECG electrode systems...

ECG monitoring is no place for compromises. That's why American offers you a choice of "no-compromise" electrode systems, each designed for a specific monitoring area.

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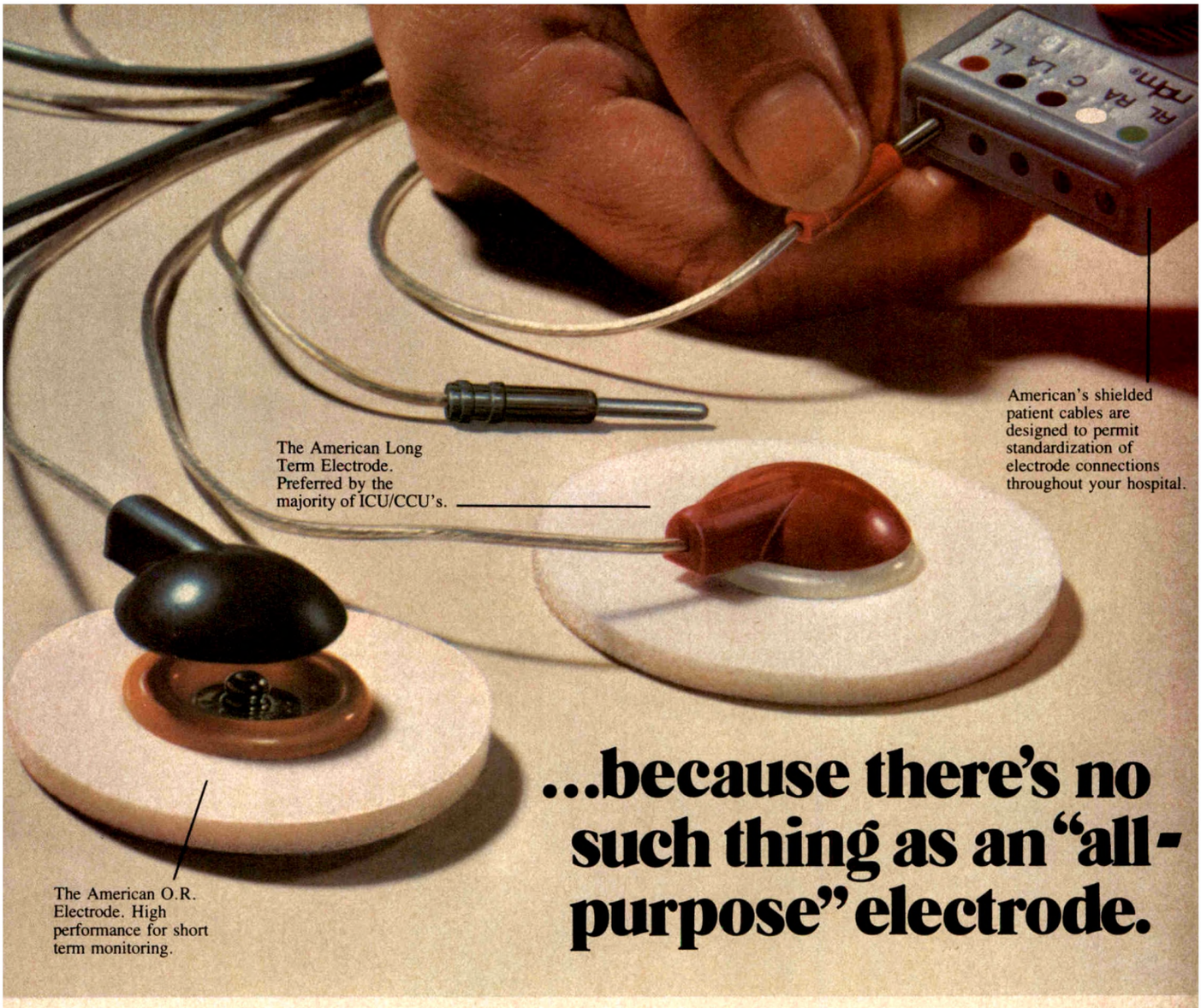
Infants are special. So is American's Infant Electrode system: It puts a premium on comfort and reliable ECG or apnea monitoring.

Despite its small size and unusually mild gel, the silver/silver chloride Infant Electrode delivers up to 72 hours of the same high performance as American's adult Long Term Electrode.

The low profile leadwire connector fastens to the electrode without putting pressure on the infant.

Like all the other systems from American, the Infant Electrode System is adaptable to monitoring units throughout the hospital. You can enjoy the benefits of a system designed solely for monitoring infants with your present ECG equipment.

For more information please write to: NDM, Department J, 3040 East River Road, Dayton, Ohio 45439.



...because there's no such thing as an "all-purpose" electrode.

Stress Test System

The American Stress Test system minimizes problems with wide or unstable base lines, motion artifact and possible hidden S-T depression.

The silver/silver chloride electrodes are quickly and easily applied . . . and they'll stay put, even on patients who perspire heavily.

The quick disconnect cable and leadwires are fully shielded: Electrical interference is virtually eliminated; a damaged leadwire need not interrupt test continuity because it can be replaced in moments.

American's system can make stress testing easier for the technician and more meaningful to the cardiologist.

(Because of the Stress Test Electrode's special gel formulation, application periods of longer than four hours are not recommended.)

Long Term™ System

The majority of ICU/CCU's in this country now depend on the American Long Term Electrode system.

There are reasons for this overwhelming acceptance. The silver/silver chloride Long Term Electrode is convenient to use and delivers up to seven days of reliable, trouble-free monitoring performance.

The things you don't want . . . patient skin irritation, motion artifact and wide base lines . . . are the things this system invariably eliminates.

The American Long Term Electrode system lets you devote more time to patient care, less time to fussing with electrodes.

O.R. Electrode

This system answers the special needs of short term monitoring in operating and recovery rooms, or wherever there's a need for high performance on a short term basis.

American's O.R. Electrode delivers a strong signal and immediate base line stability.

Best of all, this advanced electrode is fully compatible with your present monitoring equipment. With the appropriate American leadwire and cable, the electrodes used for monitoring in the O.R. can be left on the patient for monitoring in the recovery room.

Clinical Trial

There's an American ECG electrode system ideally suited to your particular monitoring requirements.

Please contact your American Hospital Supply or NDM Representative to arrange a no obligation clinical trial, including a total inservice for your staff. American will supply electrodes, leadwires and cables to adapt to your present monitoring units during the trial period.

ndm® Manufactured in U.S.A. by NDM Corporation, Dayton, Ohio 45439

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Long Term is a trademark of the NDM Corporation. American Long Term, Stress Test, Infant and O.R. electrodes are protected by the NDM Corporation by the following U.S. Patents: 3696807, 3701346, 3713435, 3820531.

Principles of oral anticoagulation

Practical Considerations

Identifying your patient at risk of thromboembolic complications

While every MI patient is not a candidate for oral anticoagulation therapy, a history of previous infarct or angina, persistent atrial fibrillation or congestive failure, severe hypotension or shock or serious arrhythmia may increase risk of thromboembolic complications.

In addition, certain procedures often place your surgical patient, particularly if he's over 40 years of age, in the high risk category—cup arthroplasty or pelvic surgery, heart valve replacement, reparative vascular surgery.

Your geriatric patient, too, is at high risk of thromboembolism if he's suffered a fracture—especially of the hip, pelvis or a lower extremity—or if his history includes venous insufficiency.

For any of these individuals, obesity, previous episodes of venous thrombosis or pulmonary embolism and a future including prolonged bed rest all increase the risk of thromboembolic complications, and make him a candidate for oral anticoagulation.

Laboratory monitoring

For every patient receiving COUMADIN® (*crystalline* sodium warfarin), frequent laboratory monitoring is a key to effective therapy. Determine prothrombin time daily until results stabilize in the therapeutic range —1½ to 2½ times normal. Individualize dosage and administration as indicated by prothrombin time results. Determine subsequent prothrombin times periodically throughout the course of therapy.

Educating your patient

Because a patient is generally more reliable if he understands his condition and his medication, he should be made aware of the factors that may influence his prothrombin time and, therefore, his response to COUMADIN®—dietary change, travel, other medication, change in physical condition and abrupt environmental change. What's more, he should know the importance of regularly taking the exact dosage of COUMADIN® prescribed and of keeping every appointment with you and with the laboratory.

COUMADIN® is an Endo U.S. registered trademark.

Therapeutic principles put into practice

COUMADIN®

CRYSTALLINE SODIUM WARFARIN*)

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional and lumbar block anesthesia.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Pregnancy–COUMADIN® passes through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage **in utero,** even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. The newborn may be particularly sensitive to sodium warfarin. There have been reports of birth malformations in children born to mothers who have been treated with warfarin during the first trimester of pregnancy. Whether warfarin was in fact the responsible agent has not been established. Therefore, women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed. If COUMADIN® must be used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks. **Lactation**–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Spinal puncture. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN®.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methylphenidate; monoamine oxidase inhibitors; nalidixic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates (in excess of 1 Gm/day); sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K-dependent factors, namely Factors VII, IX, X and II, the factors affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN® may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time; and therefore, when patients are receiving both heparin and COUMADIN®, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN® may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Water for Injection. 75 mg: Unit consists of 1 vial, 75 mg; sodium chloride, 15 mg; thimerosal, 0.3 mg. pH is adjusted with sodium hydroxide, accompanied by a 3 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

Rev. April, 1975

*Present as crystalline sodium warfarin isopropanol clathrate.

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U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

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Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
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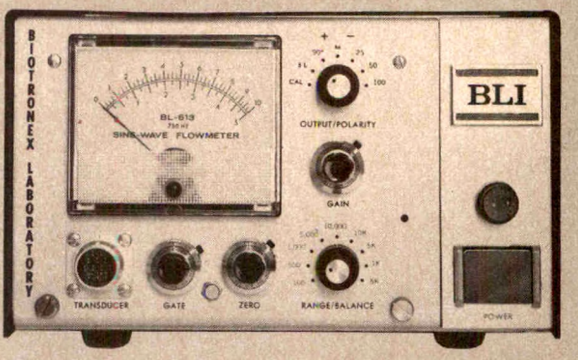
DUPONT

EDO-2620

BLI

Sine-Wave Blood Flowmeter

BL-613 with ELECTRONIC ZERO



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INTERNIST

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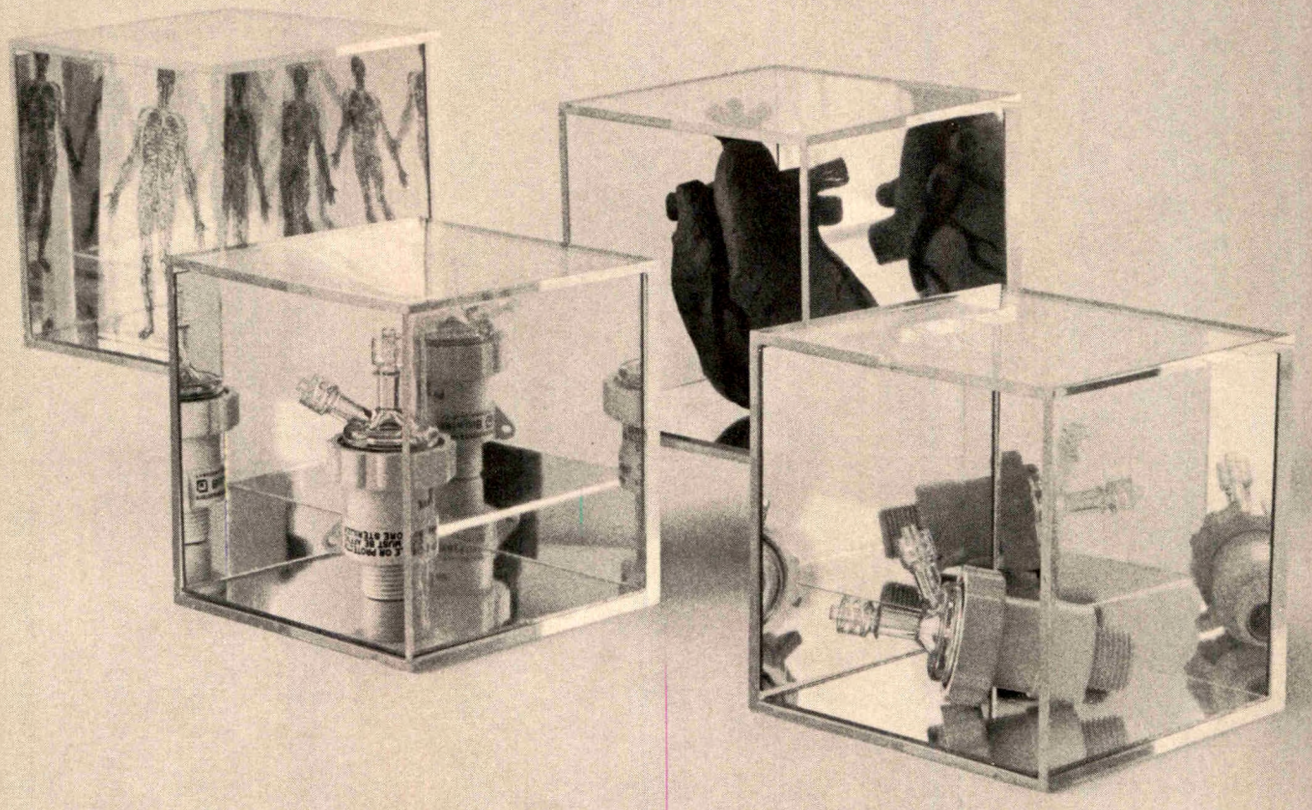
Bell & Howell's Physiological Pressure Transducer... The Cornerstone of Reliability



The building blocks of reliability — dependability, accuracy and performance — are inherent features of Bell & Howell's Model 4-327I Physiological Pressure Transducer.

Modular construction permits interchangeability of components, reducing the costs for replacement parts.

Three levels of isolation prevent the accidental introduction of electrical current.

Additionally, all units are electrically standardized.

The Model 4-327I can also be used in any position and is not damaged by use with defibrillation or electrocautery equipment.

To find out more, write us at 360 Sierra Madre Villa, Pasadena, California 91109.

CEC DIVISION

BELL & HOWELL

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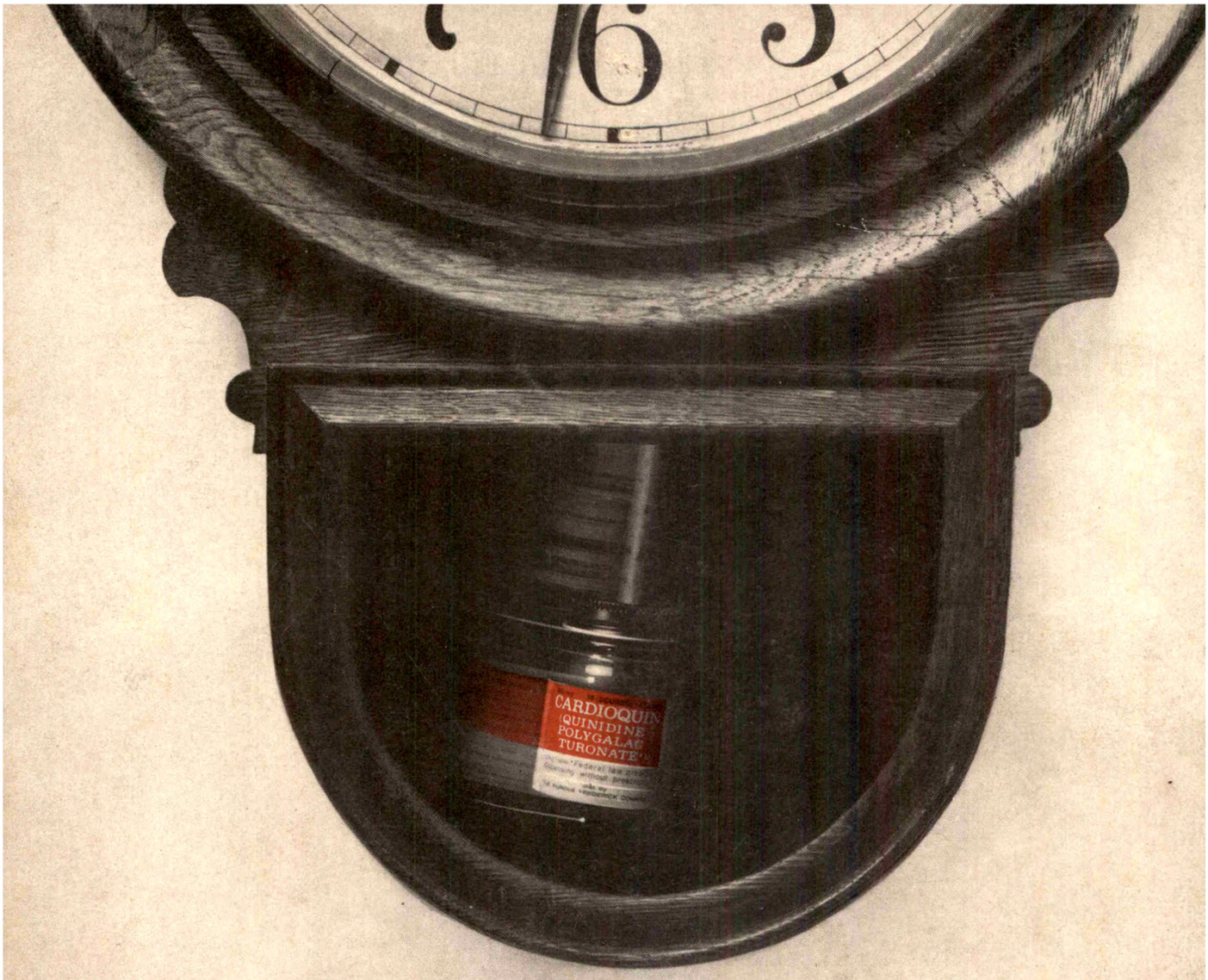

Beat after beat...day after day

CARDIOQUIN tablets

(quinidine polygalacturonate)

To convert...to MAINTAIN normal sinus rhythm

After conversion of cardiac arrhythmias—whether with CARDIOQUIN Tablets or some other current method—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required in most cases to maintain normal sinus rhythm.

Well-tolerated, CARDIOQUIN Tablets are particularly suited for maintenance therapy, since the polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heartblock; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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OCTOBER 6, 1975

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Angiographic and Hemodynamic Effects of Nitroglycerin

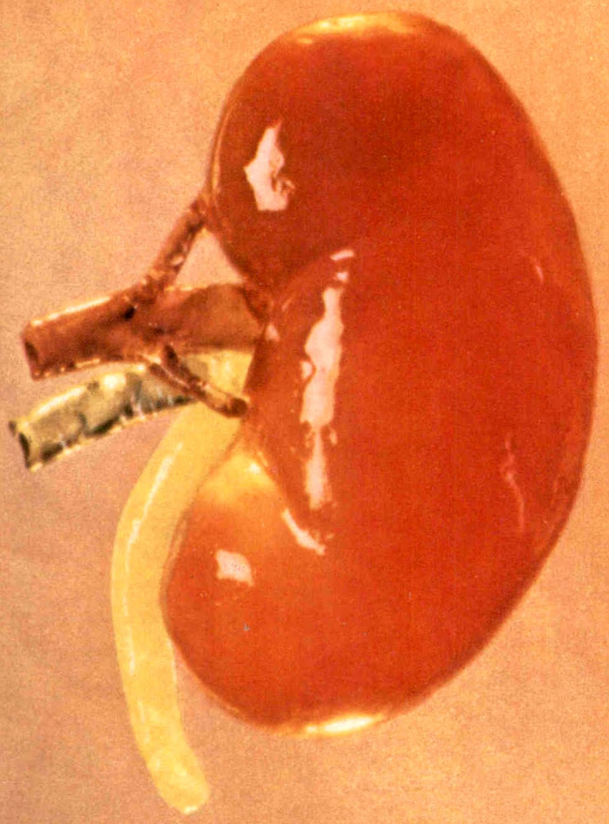
Surgery for Coronary Heart Disease in Infancy

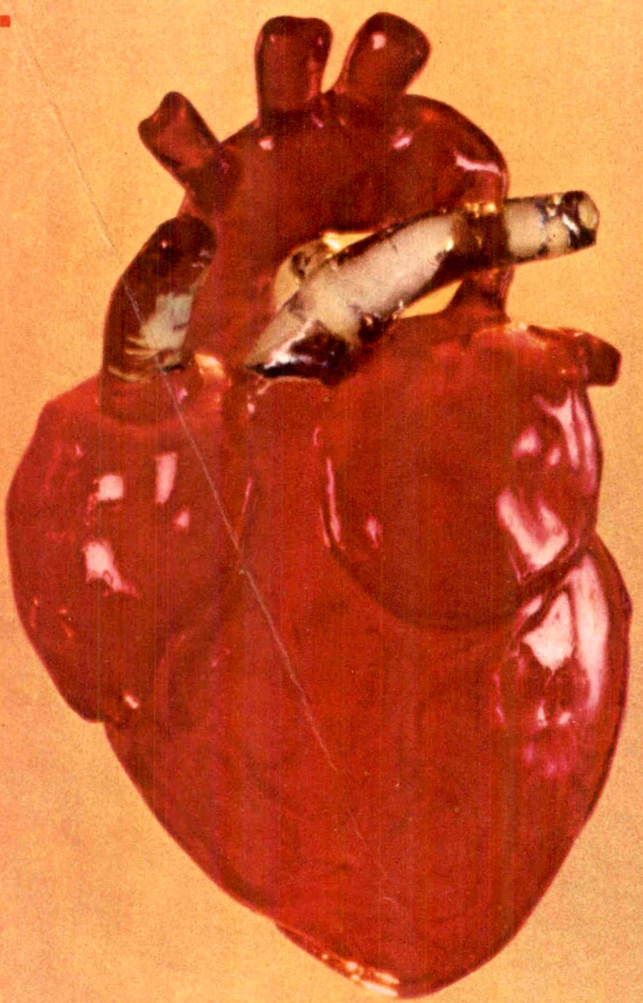
Ischemic Heart Disease: An Overview

Contents on Page A9

A YORKE MEDICAL JOURNAL

In hypertension,
ALDOMET® (METHYLDOPA|MSD)
usually offers more than effective lowering of blood pressure...



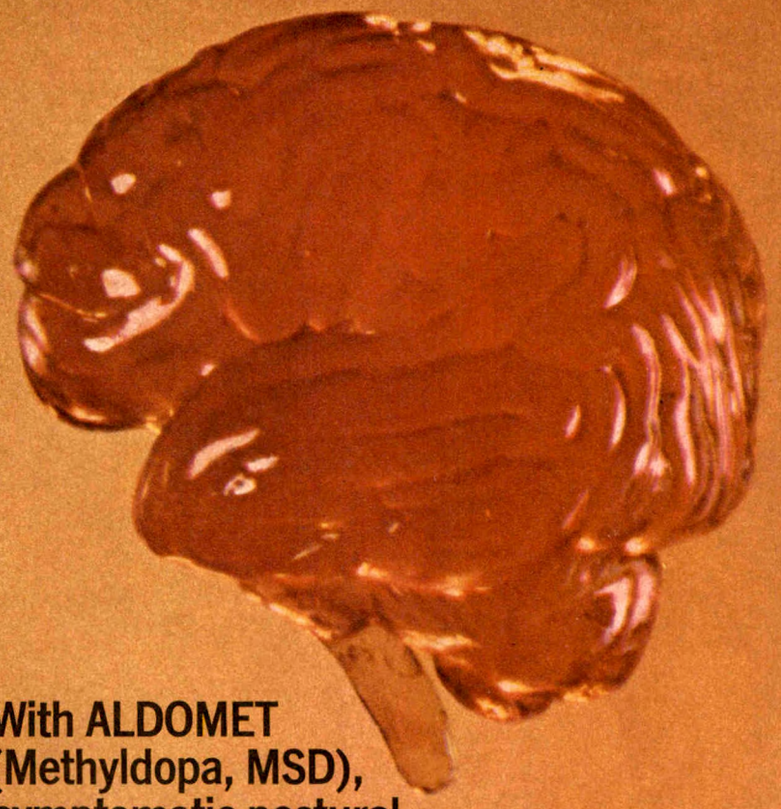


With ALDOMET (Methyldopa, MSD), existing renal function is usually unchanged

ALDOMET has no direct effect on renal function. When used in effective doses, ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction.

With ALDOMET (Methyldopa, MSD), cardiac output is generally unchanged

ALDOMET has no direct effect on cardiac function. When ALDOMET is used in effective doses cardiac output is usually maintained with no cardiac acceleration; in some patients the heart rate is slowed.



With ALDOMET (Methyldopa, MSD), symptomatic postural hypotension is infrequent

ALDOMET reduces both supine and standing blood pressure. Less frequent symptomatic postural hypotension is experienced with ALDOMET than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.

for hypertension

TABLETS, 250 mg, 500 mg, and 125 mg

ALDOMET®

(METHYLDOPA|MSD)

a unique antihypertensive agent

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders. It is not recommended in pheochromocytoma.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

MSD
MERCK SHARP & DOHME

addendum

to further simplify therapy for many patients

now available

ALDOMET® 500 mg

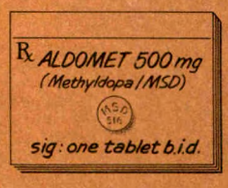
(METHYLDOPA|MSD)

- **often more practical to prescribe**
- **easier for patients to remember**

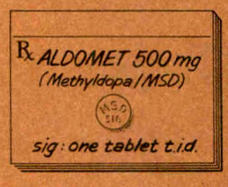
Now offered in addition to the standard 250-mg tablet, the new ALDOMET 500 mg tablet is a patient convenience. An especially important one, since in hypertension convenience of the dosage schedule is one factor that can make the difference in compliance of the patient. The minimum daily dose of ALDOMET is 250 mg b.i.d. The usual starting dose is 250 mg t.i.d. Dosage is adjusted as necessary by adding or deleting 250 mg or 500 mg at intervals of not less than two days. The maximum dose is 3.0 g per day.

Examples of b.i.d. or t.i.d. dosage convenience provided by ALDOMET 500 mg within the usual daily dosage range of 500 mg to 2.0 g:

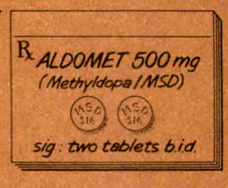
1.0-g daily dose =

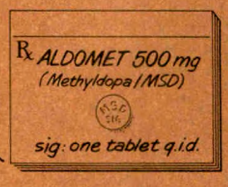


1.5-g daily dose =



2.0-g daily dose =



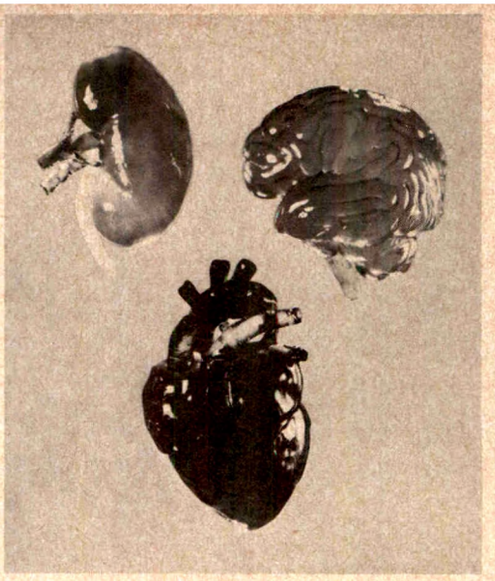


NOTE: Tablets shown are not actual size.

in hypertension

ALDOMET® (METHYLDOPA|MSD)

usually lowers blood pressure effectively



Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reaction or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, skin rash.

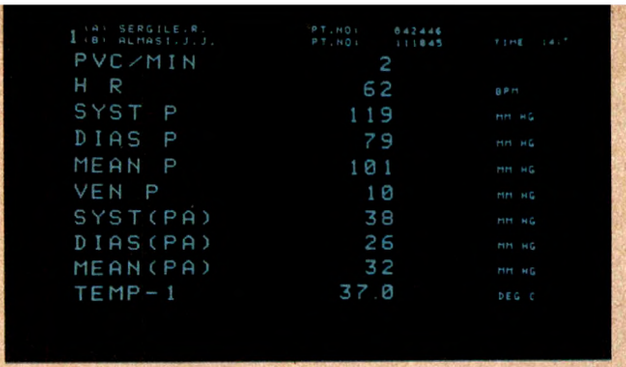
Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

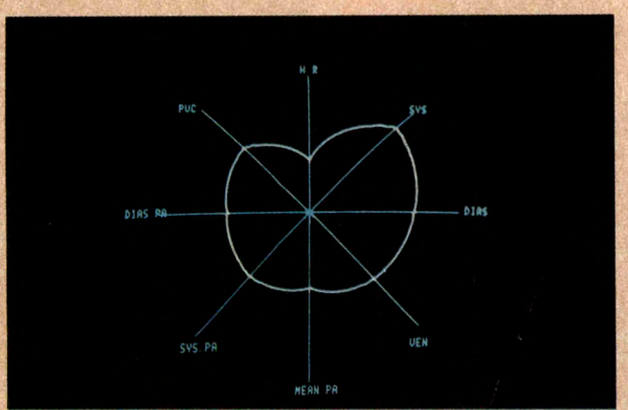
How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

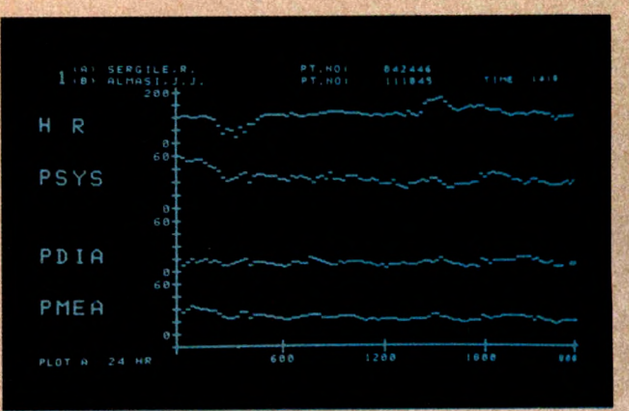
For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

MSD MERCK SHARP & DOHME



An abundance of patient data is one thing...





...a means of readily identifying data significance can be quite another.

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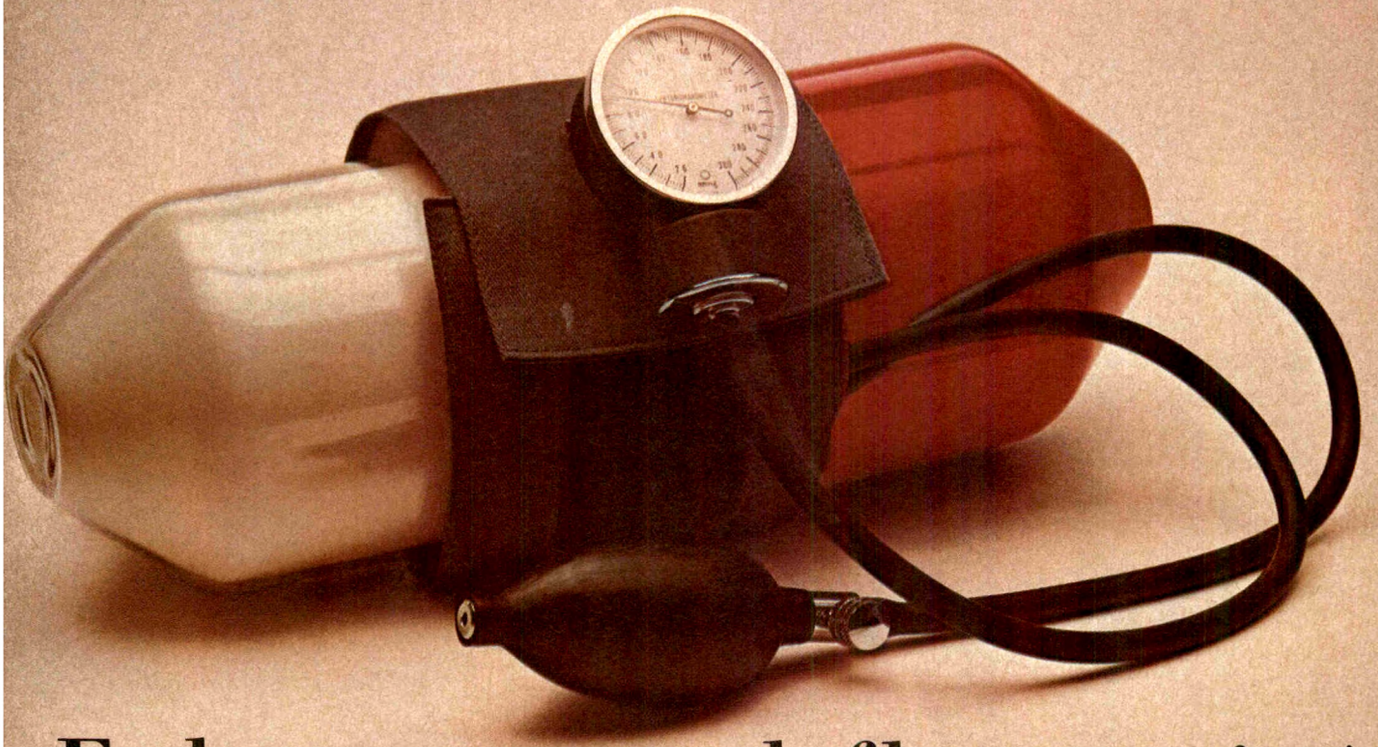

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Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

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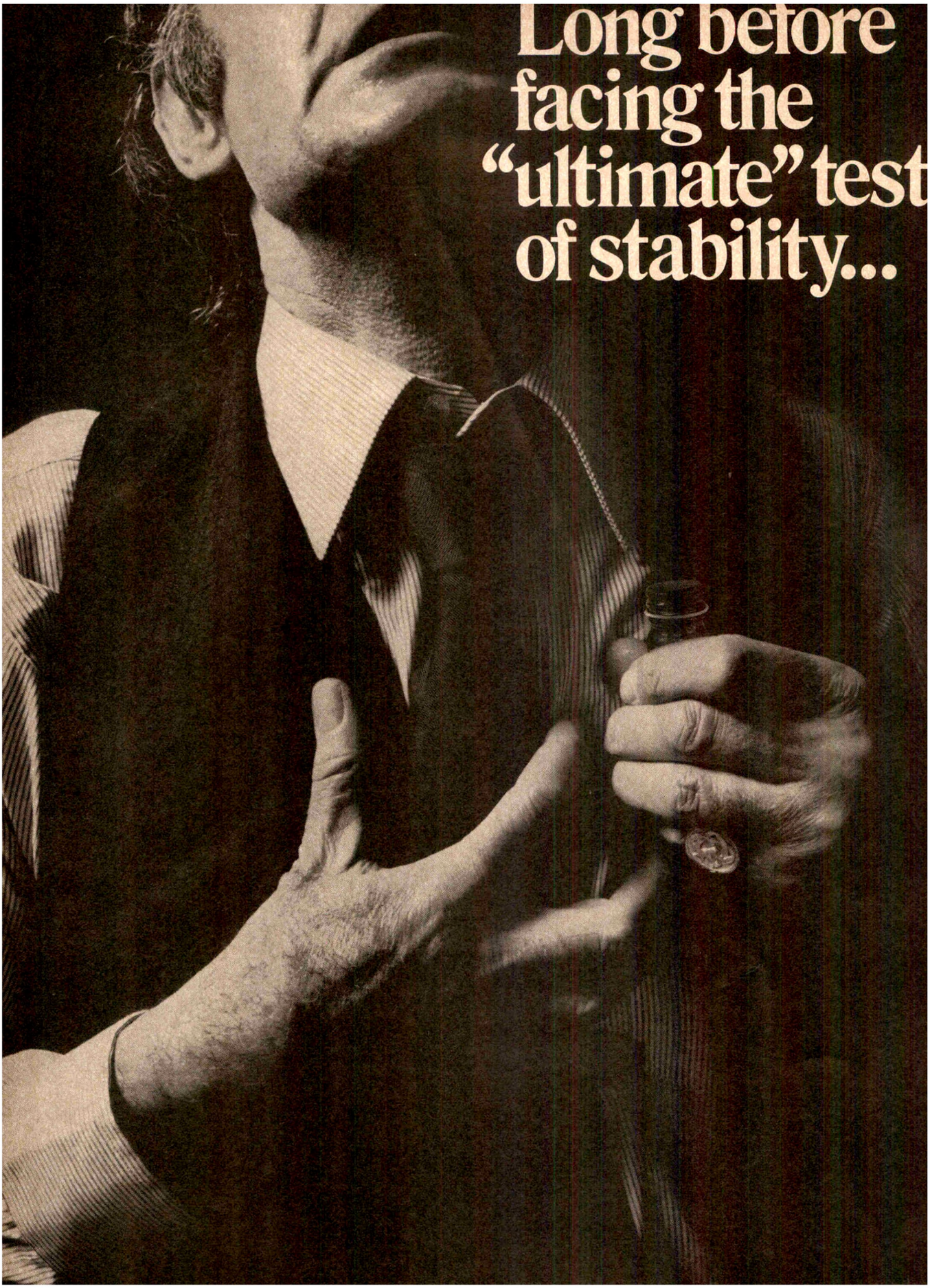
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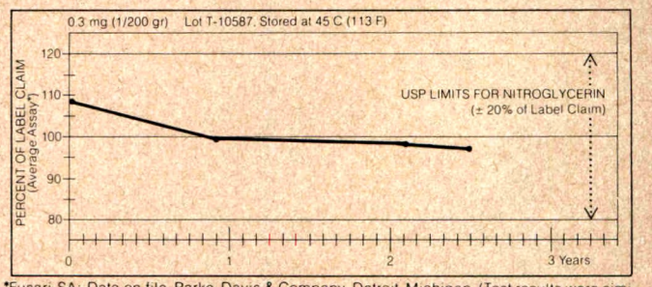

*Fusari SA: Data on file, Parke, Davis & Company, Detroit, Michigan. (Test results were similar for the 0.4-mg and the 0.6-mg strengths.)

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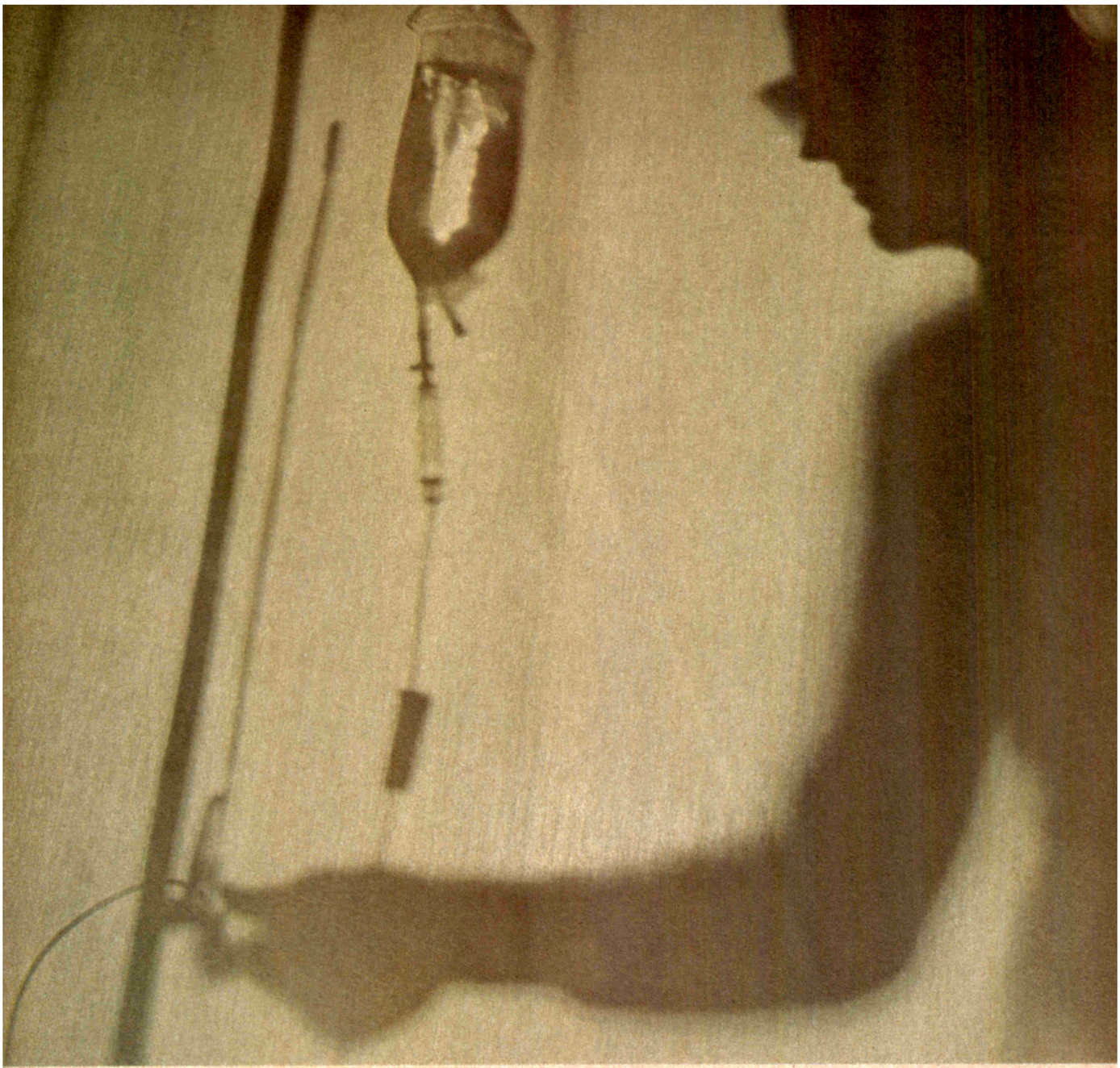

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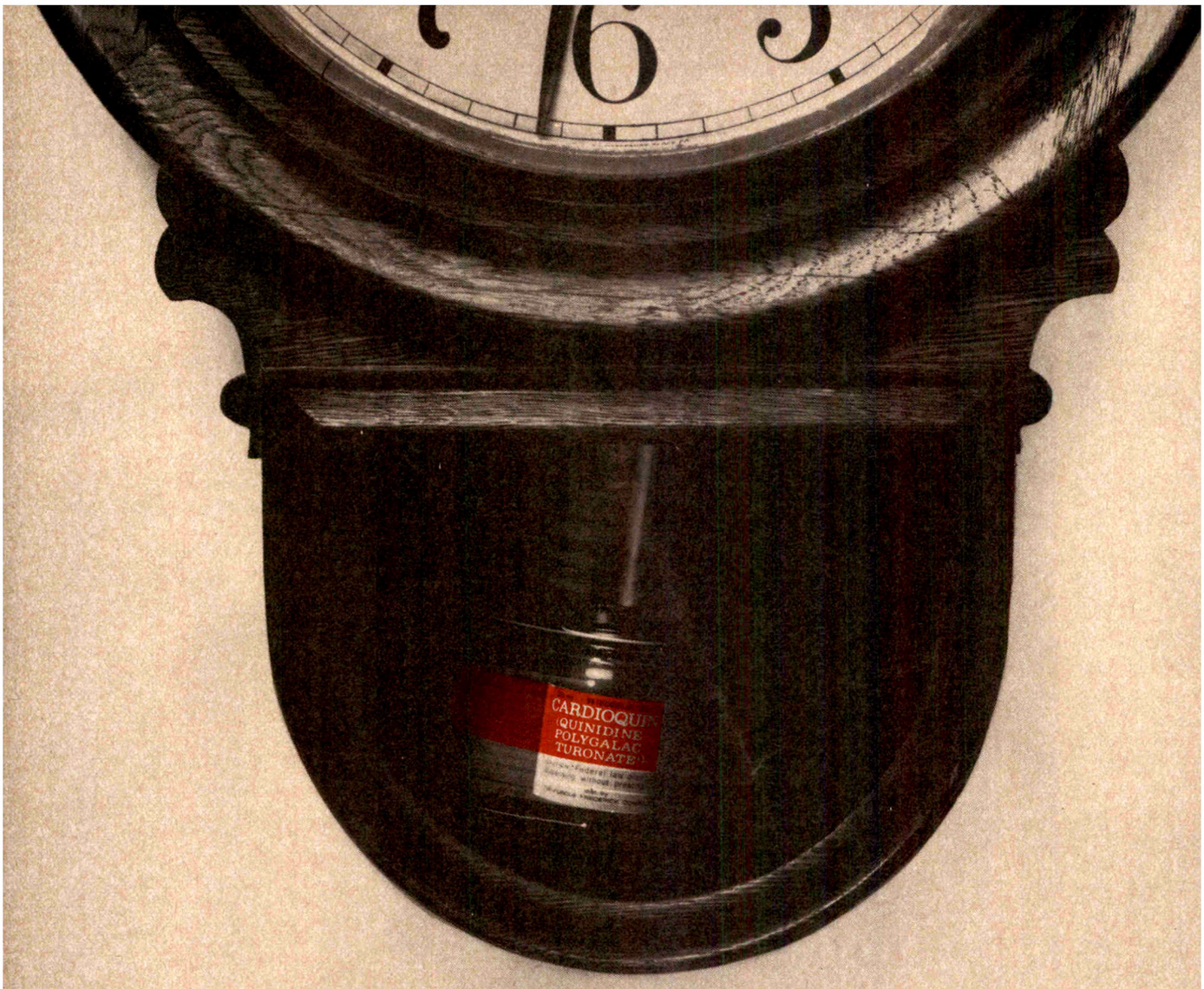

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

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JEAN G. DUMESNIL, ERIK L. RITMAN, GEORGE D. DAVIS, GERALD T. GAU, BARRY D. RUTHERFORD and ROBERT L. FRYE

After sublingual administration of 0.6 mg of nitroglycerin the mean change in derived peak rate of systolic wall thickening (peak dTw/dt) was +1.97 cm/sec in segments of the left ventricle with an initial peak dTw/dt of less than 5 cm/sec, in contrast to a change of +0.66 cm/sec in segments with an initial control value of 5 cm/sec or greater. Akinetic or dyskinetic areas did not improve. These results indicate that there is a regional myocardial response to nitroglycerin, with differing responses within the same ventricle, that depends upon the functional state of the underlying myocardium.

426 Effects of Nitroglycerin on the Major Determinants of Myocardial Oxygen Consumption. An Angiographic and Hemodynamic Assessment

HENRY GREENBERG, EDWARD M. DWYER, Jr., A. GREGORY JAMESON and BRUCE H. PINKERNELL

Data in 10 patients, of whom 7 had coronary artery disease, suggest effective reduction in heart size produced by nitroglycerin not only may diminish oxygen demand by reducing systolic wall tension, but also may improve endocardial perfusion by decreasing diastolic extravascular resistance. After nitroglycerin, the peak systolic left ventricular wall tension decreased 15 percent; heart rate increased 15 percent; mean circumferential fiber shortening velocity increased 26 percent and the ejection fraction increased 30 percent; left ventricular end-diastolic volume decreased 23 percent; and end-diastolic tension decreased 57 percent.

433 Specificity of Elevated Serum MB Creatine Phosphokinase Activity in the Diagnosis of Acute Myocardial Infarction

ROBERT ROBERTS, K. S. GOWDA, PHILIP A. LUDBROOK and BURTON E. SOBEL

The myocardium is the only human tissue containing substantial MB CPK activity. This study indicates increased serum levels of this enzyme provide a remarkably specific and sensitive reflection of myocardial injury.

438 The Functional Defect in Amyloid Heart Disease. The "Stiff Heart" Syndrome

CHRISTOPHER CHEW, GALAL MOKHTAR ZIADY, MAURICE J. RAPHAEL and CELIA M. OAKLEY

Distinctive echocardiographic, angiocardiographic and hemodynamic features of a "stiff heart," found in three subjects with heart failure due to amyloid deposits, appear to be unique to this disorder. Ultrasonic demonstration of a normal left ventricular dimension in diastole, diminished amplitude of excursion and increased systolic dimension strongly suggest amyloid. The characteristic cineangiographic appearance of the left ventricle includes greatly coarsened trabeculae, marked papillary muscle impressions and reduced systolic emptying. Hemodynamically the cardiac output is low, the left ventricular pressure shows no diastolic "dip and plateau" and there is a small atrial kick.

Continued on page A13

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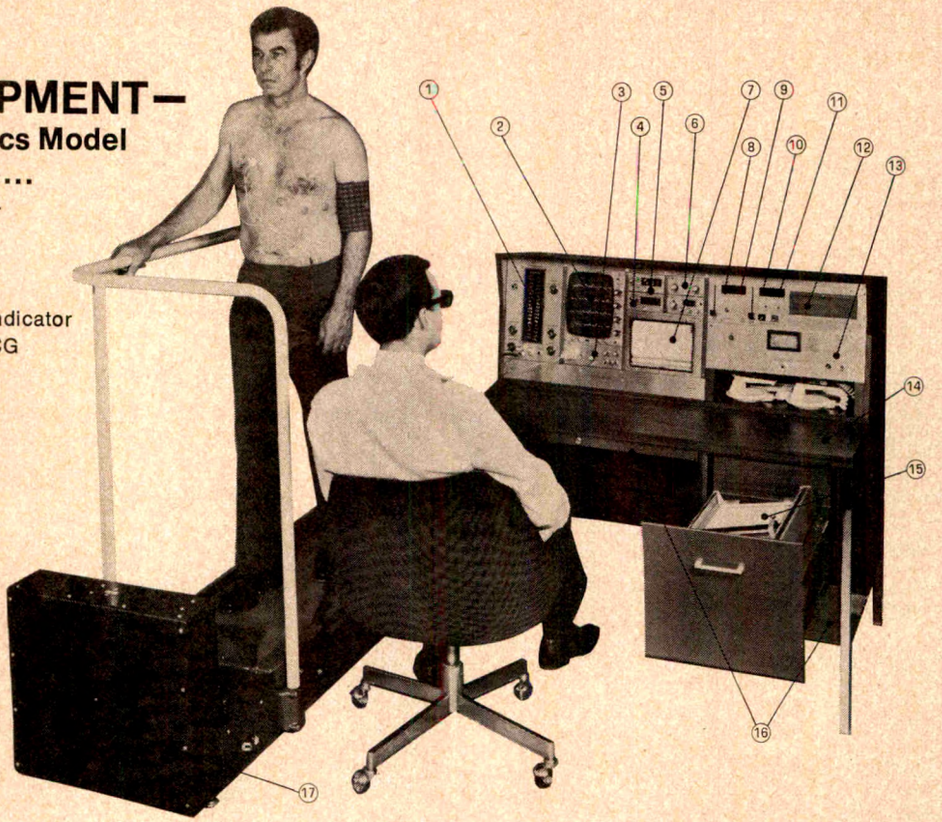

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445 Sinus Nodal Responses to Atrial Extrastimuli in Patients Without Apparent Sinus Node Disease

RAMESH C. DHINGRA, CHRISTOPHER WYNDHAM, FERNANDO AMAT-Y-LEON, PABLO DENES, DELON WU and KENNETH M. ROSEN

Scanning with an atrial extrastimulus (A_2) disclosed zones of nonreset and reset in all 36 subjects with normal sinus nodal function. Zones of interpolation and echoes were much less common. Sinoatrial conduction time (92 ± 30 msec) was long in these patients without apparent sinus node disease.

EXPERIMENTAL STUDIES

453 Nitroglycerin in Experimental Myocardial Infarction. Effects on Regional Left Ventricular Length and Tension

VIDYA S. BANKA, MONTY M. BODENHEIMER and RICHARD H. HELFANT

Nitroglycerin exerts a differential effect on the myocardium after coronary occlusion. The nonischemic zone shows significant contractile improvement manifested by an increase in tension and decrease in length; the border zone shows qualitatively similar changes of lesser magnitude; the ischemic zone is unaffected. This study supports the potential clinical usefulness of nitroglycerin in patients with acute myocardial infarction.

459 Dissociation of the Inotropic Effect of Digitalis From Its Effect on Atrioventricular Conduction

YOUNG I. KIM, R. JOE NOBLE and DOUGLAS P. ZIPES

Data obtained in open chest dogs indicate a dissociation between the effects of digitalis on contractility and atrioventricular (A-V) dissociation. Digitalis acts on the ventricular contractile mechanism in a direct, linear fashion and on A-V nodal transmission as a nonlinear response that is mediated mainly through the autonomic nervous system. The optimal dose and serum level of digitalis needed to treat congestive heart failure may therefore differ from those needed to treat supraventricular tachycardias.

METHODS

468 Improved Diagnosis in Coronary Cinearteriography with Routine Use of 110° Oblique Views and Cranial and Caudal Angulations. Comparison with Standard Transverse Oblique Views in 100 Patients

HAROLD E. ALDRIDGE, MICHAEL J. McLOUGHLIN and KENNETH W. TAYLOR

Of 100 patients undergoing coronary arteriography, use of the Siemen's Cardioskop-U unmasked in 20 percent additional lesions that would have been missed by conventionally mounted X-ray systems, significantly improved the diagnosis in another 34 percent and detected lesions in 4 of 12 patients with apparently normal arteriograms in standard projections.

474 Comparison of Observer Performance with 16 mm Cinefluorography and 70 mm Camera Fluorography in Coronary Arteriography

LARS BJÖRK, HUGO SPINDOLA-FRANCO, FRANCIS X. VAN HOUTEN, PETER F. COHN and DOUGLASS F. ADAMS

There were significant inter- and intraobserver differences in assessing the degree of coronary arterial stenosis by means of clinical 16 mm cinefluorography and 70 mm camera fluorography. Interobserver variation in detecting collateral circulation was small. Coronary arteriography remains a semiquantitative method whose reliability is increased by the use of more than one observer.

Continued on page A15

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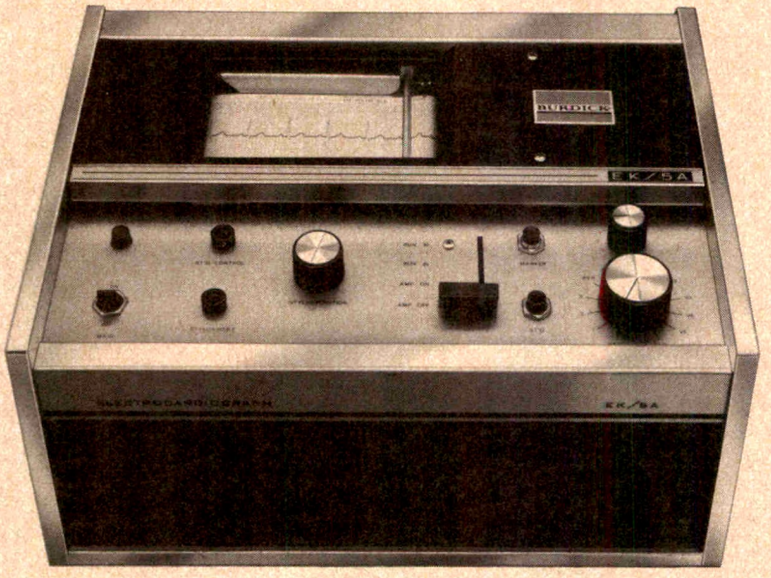

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PEDIATRIC CARDIOLOGY

479 Survival After Systemic to Pulmonary Arterial Shunts in Infants Less Than 30 Days Old with Obstructive Lesions of the Right Heart Chambers

KALIM UDDIN AZIZ, PETER M. OLLEY, RICHARD D. ROWE, GEORGE A. TRUSLER and WILLIAM T. MUSTARD

In a group of 97 infants less than 30 days old with obstructive lesions of the right heart chamber undergoing palliative surgery between 1950 and 1972, the overall surgical mortality rate was 34 percent in the 61 patients seen after 1965 and 78 percent in the 36 patients seen before 1965. The surgical mortality rate in infants operated on during the 1st week of life was double that of infants operated on in the 2nd through 4th weeks. Primary repair is preferable if the risk approximates that of palliative procedures.

484 Results of Pulmonary Arterial Banding in Infancy. Survey of 5 Years' Experience in the New England Regional Infant Cardiac Program

KENNETH J. DOOLEY, LUCY PARISI-BUCKLEY, DONALD C. FYLER and ALEXANDER S. NADAS

The overall survival rate to age 1 year was 63 percent in 238 infants subjected to pulmonary arterial banding. Survival was least likely (37 percent) in those who required banding in the 1st month of life. Banding is recommended primarily for infants with defects potentially correctable after the 1st year of life. Ten percent of the infants in this series had lesions presently considered uncorrectable and their survival rate was poor, less than one third reaching their first birthday.

489 Considerations in the Surgical Management of Infantile Coarctation of Aorta

JOHN P. CONNORS, ALEXIS F. HARTMANN, Jr. and CLARENCE S. WELDON

Modifications in operative and postoperative care, including microsurgical techniques, careful approximation of the aortic lumen with interrupted sutures, prolonged ventilatory support postoperatively, controlled positive airway pressure and continued aggressive medical therapy for heart failure, have significantly reduced the operative mortality rate from 38 to 17 percent and the incidence rate of significant restenosis from 60 to 33 percent in infants with infantile coarctation of the aorta.

493 Cardiac Catheterization in Small Infants: The Percutaneous Approach

JOHN H. GAY

With use of the technique described in this report, percutaneous sheath cardiac catheterization proved successful in 90 percent of 20 infants weighing less than 4.2 kg. This technique is quickly performed, preserves venous integrity, has a low rate of morbidity, minimizes formation of scar tissue, reduces infection and is readily acceptable to the patient and his parents.

REVIEWS

496 Ischemic Heart Disease: An Overview

RICHARD S. ROSS

In patients with ischemic heart disease coronary arterial surgery improves the quality of life by reducing symptoms, but there is no convincing evidence that it improves ventricular function or increases survival time. Increased blood flow to the ischemic area, infarction of ischemic myocardium or the nonspecific effects of surgery may account for the improvement. The prevention of coronary arteriosclerosis is considered a preferable and attainable long-term solution to the problem of ischemic heart disease.

Continued on page A17

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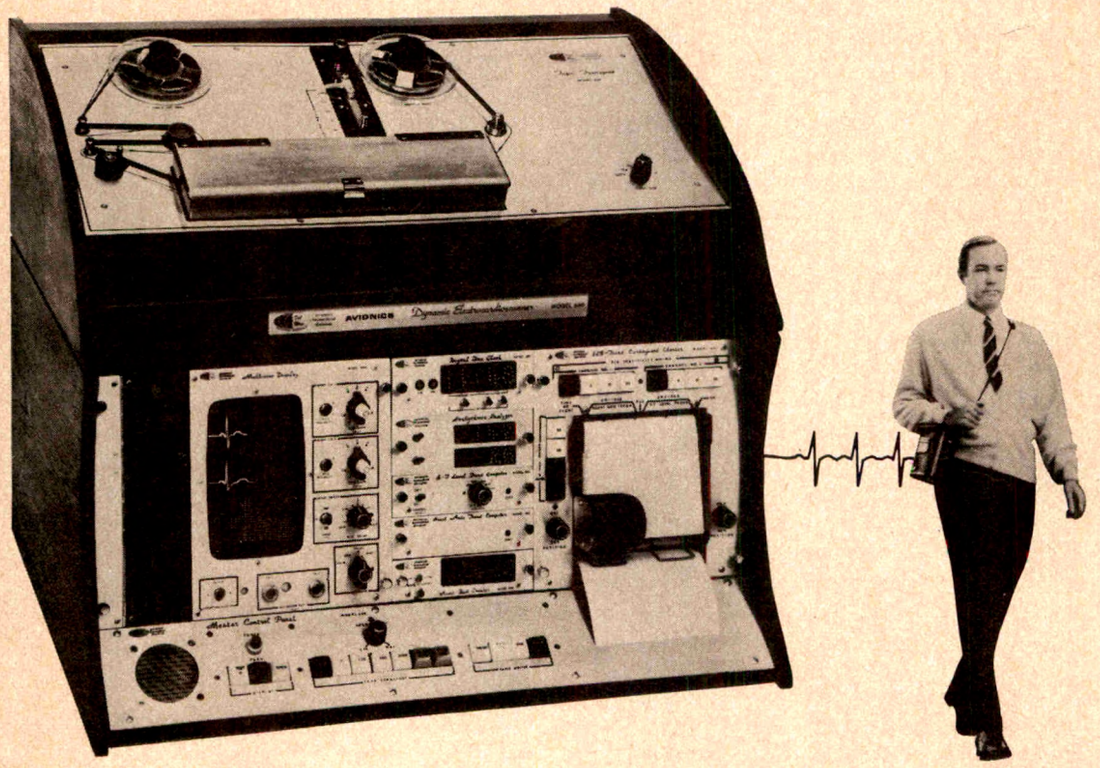

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HISTORICAL MILESTONES

506 Experiments on Heart Valves (1908) by Harvey Cushing and J. R. B. Branch

SAUL JARCHO

Not to be overlooked in the glow of today's golden era of cardiac surgery are the experiments on canine heart valves performed late in the 19th century that led Cushing and Branch, the authors of these excerpts, as well as Brunton, to envision clearly and practically the surgical attack on valvular disease in man. These excerpts summarize the beginnings of such cardiac surgery.

CASE REPORTS

509 Coronary Insufficiency in Children. Coronary Arteriographic Studies in Two Siblings From a Family with Hyperbetalipoproteinemia

DAVID BIALOSTOZKY, MARTIN LUENGO, CLEMENTINA MAGOS and EDUARDO ZORRILLA

Homozygous type II hyperbetalipoproteinemia, characterized by a high serum level of low density lipoprotein (LDL), is highly atherogenetic. In the M family with this familial disorder, one 11 year old boy had progressive obstruction of two coronary arteries, angina pectoris, myocardial infarction, cardiomegaly and congestive heart failure over a 2 year period. A 9 year old sister with apparently normal coronary arteries remains asymptomatic. Other family members showed cardiovascular stigmata of this familial genetic disorder, found in 1 of every 150 to 200 live births.

515 Coronary Artery Disease in an 18 Year Old Girl with Pseudoxanthoma Elasticum: Successful Surgical Therapy

JOHN M. BETE, JOHN S. BANAS, Jr., JOHN MORAN, VIVIAN PINN and HERBERT J. LEVINE

A triple coronary artery-saphenous vein bypass graft was successfully performed with good results in an 18 year old girl with pseudoxanthoma elasticum, angina pectoris for 8 years and an old anteroseptal myocardial infarction. The patient became asymptomatic and able to resume a more normal life, including marriage and pregnancy.

521 Multiple Ventricular Aneurysms

BABASOLA O. OKUWOBI

Most patients with multiple ventricular aneurysms, like this 17 year old Nigerian girl without symptoms of cardiac disability, have been African Negroes free of coronary artery disease. After presenting with ventricular tachycardia that reverted to normal after an intravenous injection of 50 mg of lidocaine, this girl remained clinically well. The pathogenesis of this unusual condition is uncertain.

524 Herniation of Mitral Leaflets in the Ehlers-Danlos Syndrome

KENNETH D. BRANDT, ROBERT D. SUMNER, THOMAS J. RYAN and ALAN S. COHEN

The "floppy valve" syndrome, a common feature of Marfan's syndrome, may also occur in patients with other heritable disorders of connective tissue. This report describes a 47 year old man with typical Ehlers-Danlos syndrome and mitral regurgitation arising from atrial herniation of the posterior leaflet of the mitral valve.

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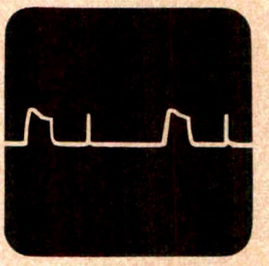

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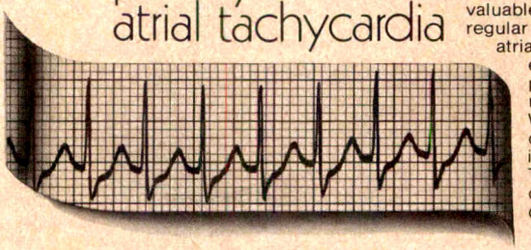
in the inner circle of
Inderal® stands out

The place of INDERAL (propranolol hydrochloride) among the standard drugs for the treatment of disturbed cardiac rhythm has been frequently reaffirmed throughout seven years of clinical use. In fact, after withdrawal of digitalis, "...it may be the treatment of choice for digitalis-induced arrhythmias, provided hypokalemia is not present."[1] It has been widely used in selected supraventricular arrhythmias that have proved resistant to digitalis and in tachyarrhythmias precipitated by exercise, emotional stress, or undesirable sympathetic stimulation; and it is also effective in controlling supraventricular tachyarrhythmias related to the Wolff-Parkinson-White syndrome.[2]

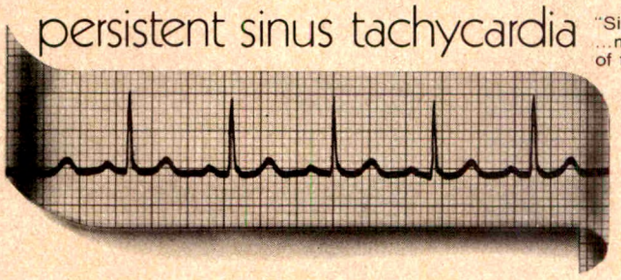
INDERAL protects the heart from undesirable catecholamine stimulation through its beta blocking action. Propranolol occupies the beta-receptor sites, making them unavailable to the beta-adrenergic stimulating effects of catecholamines. INDERAL is the first beta-adrenergic blocking agent in clinical cardiologic use.

paroxysmal atrial tachycardia



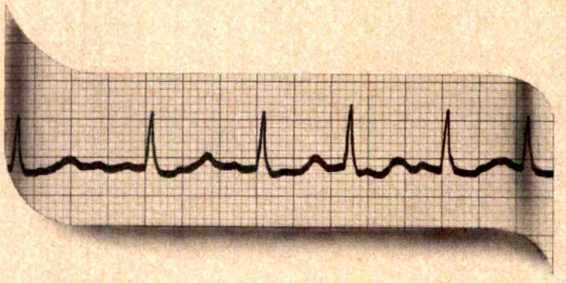
"In paroxysmal atrial tachycardia, the dru slows the ventricular rate, and also valuable in restoring the heart to regular sinus rhythm."[3] "Paroxysm atrial tachycardia induced by e ercise...has uniformly bee prevented by propranolol," ar results with INDERAL in th Wolff-Parkinson-White syn drome "...have been favorab in all but a few patients reporte This condition appears to b one of the more definite ind cations for propranolol."[4]

persistent sinus tachycardia



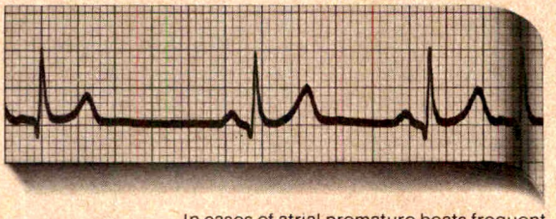
"Sinus tachycardia induced by stress ...may be inappropriate to the needs of the patient and, in fact, may be causing symptoms of itself. If the clinical situation does not suggest a needed compensatory sinus tachycardia and the heart rate is indeed inappropriate, treatment with propranolol has been successful."[4]

tachycardias and arrhythmias due to thyrotoxicosis



Although propranolol may accomplish only the reduction of the heart rate in hyperthyroidism, it has proved useful for this purpose. "Sinus tachycardia in hyperthyroidism which causes symptoms may be relieved by the administration of propranolol before definitive therapy....The author has observed that atrial fibrillation complicating hyperthyroidism was easily terminated using modest doses of propranolol."[4]

persistent atrial extrasystoles



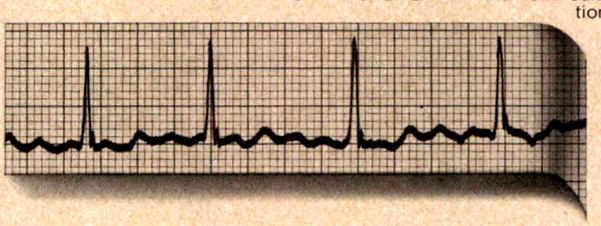
In cases of atrial premature beats frequent enough that they could herald the onset of atrial fibrillation, it has been recommended that propranolol be used after other measures have failed to control the beats.[5]

antiarrhythmia agents for supraventricular arrhythmias

atrial flutter

"In the presence of atrial flutter, ventricular rate is often difficult to control, and, as with an atrial fibrillation, propranolol hydrochloride should be added when the flutter is not controlled by digitalis, especially in the presence of mitral valve disease."[6]

atrial fibrillation

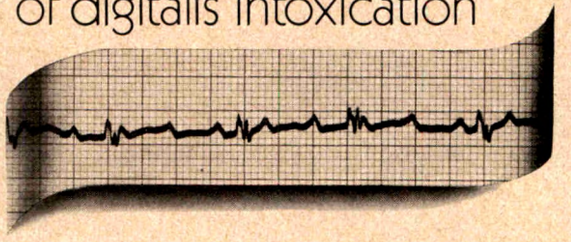


"One salutary effect of propranolol is slowing of the ventricular rate in atrial flutter and fibrillation."[4] In a review of the literature, it was noted that most patients with fibrillation not controlled by digitalis alone experienced slowing of the ventricular rate after administration of propranolol and a few reverted to sinus rhythm.[7]

---

and for tachyarrhythmias of digitalis intoxication

"Propranolol is very effective in treating arrhythmias caused by digitalis excess. Its use in this setting may be limited by the presence of significant congestive heart failure or heart block, both of which can be potentiated by propranolol. However, if given in small doses with careful monitoring, it is often of great value in the treatment of digitalis toxicity."[5]



References 1. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 2. Chung, E.K.: Postgrad. Med. *53*:107 (Apr.) 1973. 3. Harrison, D.C.: Clinical Guide to the Use of Beta-Adrenergic Blockade in Arrhythmias, Ayerst Laboratories, 1971, p. 10. 4. Reynolds, E.W.: Geriatrics *26*:150 (Feb.) 1971. 5. Helfant, R.H.: Med. Times *98*:118 (Jan.) 1970. 6. Sonnenblick, E.H.: Arrhythmias and Beta-Adrenergic Blockade, Ayerst Laboratories, 1971, p. 7. 7. Gibson, D., and Sowton, E.: Prog. Cardiovasc. Dis. *12*:16 (July) 1969.

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BRIEF SUMMARY
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propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

INDICATIONS:

Cardiac Arrhythmias

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is non-compensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.
May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias
Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias
With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication
If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.) Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia.
Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis
INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma
After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effect of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

When discontinuance of chronically administered INDERAL is planned, the dosage should be gradually reduced over a period of several weeks and the patient should continue to be carefully monitored. There have been reports of myocardial infarction occurring in angina pectoris patients following *abrupt* discontinuation of INDERAL therapy.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The oral route of administration is preferred.

ORAL

ARRHYTHMIAS—10-30 mg. three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg. three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg. daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg. administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg. (1 cc.) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED: BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride) TABLETS No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

INJECTABLE No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH js adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

Ayerst.

AYERST LABORATORIES
New York, N.Y. 10017

7420

Schering

Stat regimen for rapid reduction of blood pressure in malignant hypertension

direct-action **Hyperstat®** I.V.
Brand of DIAZOXIDE
INJECTION
20 ml. ampule
contains 300 mg

"The injection of the [diazoxide] bolus in 10 to 15 seconds results in a prompt blood pressure fall in a high percentage of cases. A maximal blood pressure response usually occurs within 5 to 10 minutes."*

☐ **Rapid reduction to normotensive levels**

Induces rapid reduction of blood pressure generally within 5 minutes... often in 1 or 2 minutes to the lowest level achieved. Blood pressure response facilitated by appropriate diuretic therapy.

☐ **Prolonged activity**

A single injection of HYPERSTAT I.V. generally maintains blood pressure below pretreatment levels for periods up to 12 hours.

☐ **Protective action—helps avert target organ damage**

Cardiac output increases as diastolic pressure is reduced. Coronary and cerebral blood flow maintained. Increased renal blood flow after transient decrease.

☐ **Uncomplicated procedure**

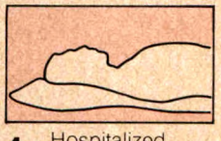
Simple I.V. "push" in a peripheral vein in 30 seconds or less. Close monitoring at frequent intervals is necessary until blood pressure is stabilized (generally 15-30 minutes). Thereafter, hourly measurement should be taken during the balance of effect.

☐ **Stable...convenient...no preparation**

HYPERSTAT I.V. Injection supplied in a 20 ml. ampule containing a stable solution of diazoxide 300 mg. ...ready to use.

*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J 87*(6): 791-795, June 1974.

Administration guidelines



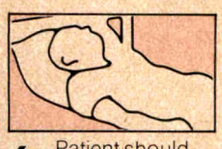
1. Hospitalized patient should be recumbent.

2. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml. ampule contains 300 mg. diazoxide).

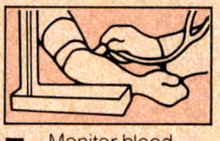
3. Insert needle only into a peripheral vein.

4. Inject entire dose I.V. in 30 seconds or less.

5. Remove needle carefully—avoid extravasation.

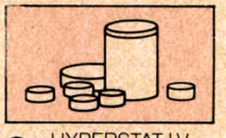


6. Patient should remain recumbent for at least half an hour after injection.



7. Monitor blood pressure closely until stabilized—usually 15-30 minutes.

8. If patient is to be ambulatory, blood pressure should be measured in standing position before surveillance is ended.



9. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective—generally within a few days.

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Before prescribing HYPERSTAT I.V. Injection, please consult complete product information on next page

Stat regimen for rapid reduction of blood pressure in malignant hypertension

direct-action **Hyperstat®** I.V.
Brand of DIAZOXIDE
INJECTION
20 ml. ampule
contains 300 mg

FOR INTRAVENOUS USE IN HOSPITALIZED PATIENTS ONLY

Description HYPERSTAT I.V. Injection is a rapidly acting antihypertensive agent. Each ampule (20 ml.) contains 300 mg. diazoxide, a nondiuretic benzothiadiazine derivative, in a clear, colorless, aqueous solution; the pH is adjusted to approximately 11.6 with sodium hydroxide. Diazoxide is 7-chloro-3-methyl-2H 1, 2, 4-benzothiadiazine 1, 1-dioxide.

Actions HYPERSTAT I.V. Injection produces a prompt reduction in blood pressure by relaxing smooth muscle in the peripheral arterioles. Cardiac output is increased as blood pressure is reduced by diazoxide; coronary and cerebral blood flow are maintained. Renal blood flow is increased after an initial decrease. Diazoxide has no known direct action on the central nervous system.

Patients refractory to other antihypertensive agents usually remain responsive to diazoxide.

Diazoxide is extensively bound to serum protein (>90%). The plasma half-life is 28 ±8.3 hours; however, the duration of its antihypertensive effect is variable, generally lasting less than 12 hours. Although an antihypertensive response has been obtained with slow intravenous injection, in general, a greater antihypertensive effect is obtained with rapid intravenous administration.

Indications HYPERSTAT I.V. Injection is indicated for the emergency reduction of blood pressure in malignant hypertension in hospitalized patients, when prompt and urgent decrease of diastolic pressure is required. Treatment with orally effective antihypertensive agents should be instituted as soon as the hypertensive emergency is controlled.

HYPERSTAT (diazoxide) I.V. Injection is ineffective against hypertension due to pheochromocytoma.

Contraindications HYPERSTAT I.V. Injection should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt.

The drug should not be used in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

Warnings **Usage in Pregnancy:** The safety of HYPERSTAT I.V. Injection in pregnancy has not yet been established.

Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults.

Usage in Children: The safety of HYPERSTAT I.V. Injection in children has not yet been established.

Hypotension may occasionally result from the administration of HYPERSTAT I.V. If hypotension severe enough to require therapy occurs, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine.

Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide.

Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. It should be noted that concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions).

Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent.

Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

Precautions HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available when HYPERSTAT I.V. Injection is used.

HYPERSTAT I.V. Injection should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively.

Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response.

As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental.

Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection.

Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

Adverse Reactions

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial and/or cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; unconsciousness, convulsions, paralysis, or confusion; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported.

Other adverse reactions: Nausea, vomiting, and/or abdominal discomfort; vasodilative phenomena, such as flushing, generalized or localized sensations of warmth, headache (sometimes throbbing), and sweating; orthostatic hypotension, lightheadedness, and weakness of short duration; supraventricular tachycardia and palpitation; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; nonanginal "tightness in the chest"; warmth or pain along the injected vein; cellulitis without sloughing and/or phlebitis at the site of extravasation; anorexia and alteration of taste; ileus; bradycardia; back pain; chest discomfort; dyspnea, choking sensation; apprehension or anxiety, malaise, and blurred vision occurred on single occasions; parotid swelling, salivation, lacrimation; ringing in the ears; diarrhea and constipation; increased nocturia; euphoria.

Drug Interactions Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

Overdosage Overdosage of HYPERSTAT I.V. Injection may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy of hyperglycemia.

Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

Animal Pharmacology and Toxicology In studies involving a number of species, including the rat, cat, dog, and monkey, diazoxide has been shown to exert significant antihypertensive actions through its direct effect on peripheral arterioles, which neither impairs cardiac function nor seriously diminishes perfusion of kidneys. In addition, in each species tested, including the rat, dog, and monkey, diazoxide elicits hyperglycemia, increased serum-free fatty acids and decreased plasma insulin levels by a mechanism thought to involve both suppression of insulin release and enhanced catecholamine action.

Although the data are not conclusive, reproduction and teratology studies in several species of animals indicate that diazoxide, when administered during the critical period of embryo formation, may interfere with normal fetal development, possibly through altered glucose metabolism. Parturition was occasionally prolonged in animals treated at term.

Dosage and Administration HYPERSTAT I.V. Injection is administered undiluted and rapidly by intravenous injection. It should only be given into a peripheral vein. Do not administer it intramuscularly, subcutaneously, or into body cavities. Avoid extravasation of the drug into subcutaneous tissues.

The response to HYPERSTAT I.V. Injection varies from patient to patient. Generally, blood pressure decreases within five minutes, often within one to two minutes, to the lowest level achieved. The blood pressure increases relatively rapidly in the next ten to 30 minutes, and then more slowly over the following two to 12 hours, nearly reaching but rarely exceeding the pretreatment level. The response to successive injections is frequently better than that to the initial injection.

Treatment of hypertensive emergencies with HYPERSTAT I.V. Injection should be limited to a few days and a regimen of oral antihypertensive medications should be instituted as soon as possible.

With the patient recumbent, the contents of one 20 ml. ampule containing 300 mg. of HYPERSTAT I.V. Injection are administered intravenously in 30 seconds or less. Slow intravenous injection may fail to reduce the blood pressure or may produce an exceedingly short response.

Specific dosage is required in children or in unusually large or small patients. This dosage may be calculated on the basis of 5 mg./kg. body weight (0.3 ml./kg.) (See Warnings).

A second administration of HYPERSTAT (diazoxide) I.V. Injection may be required for a satisfactory reduction in blood pressure, if the first injection fails to give an adequate response within 30 minutes.

Repeated administration of HYPERSTAT I.V. Injection at intervals of four to 24 hours usually will maintain the blood pressure below pretreatment levels until a regimen of oral antihypertensive medication becomes effective. The interval between injections may be adjusted by the duration of the response to each injection. It is usually unnecessary to continue treatment with HYPERSTAT I.V. Injection for more than four to five days.

Following the use of HYPERSTAT I.V. Injection, the blood pressure should be monitored closely until it has stabilized. Thereafter, measurements taken hourly during the balance of the effect will indicate any unusual response. A further decrease in blood pressure at 30 minutes or more after injection should be investigated for causes other than the action of HYPERSTAT I.V. Injection. It is preferable that the patient remain recumbent for half an hour after injection. In ambulatory patients, the blood pressure should be measured with the patient standing before surveillance is ended.

Since repeated administration of HYPERSTAT I.V. Injection can lead to sodium and water retention, administration of a diuretic may be necessary both for maximal blood pressure reduction and to avoid congestive failure.

How Supplied HYPERSTAT I.V. Injection is supplied in a 20 ml. ampule containing diazoxide 300 mg. in a clear, colorless aqueous solution; box of one ampule.

Protect from light and freezing.

Store away from heat.

AUGUST 1973

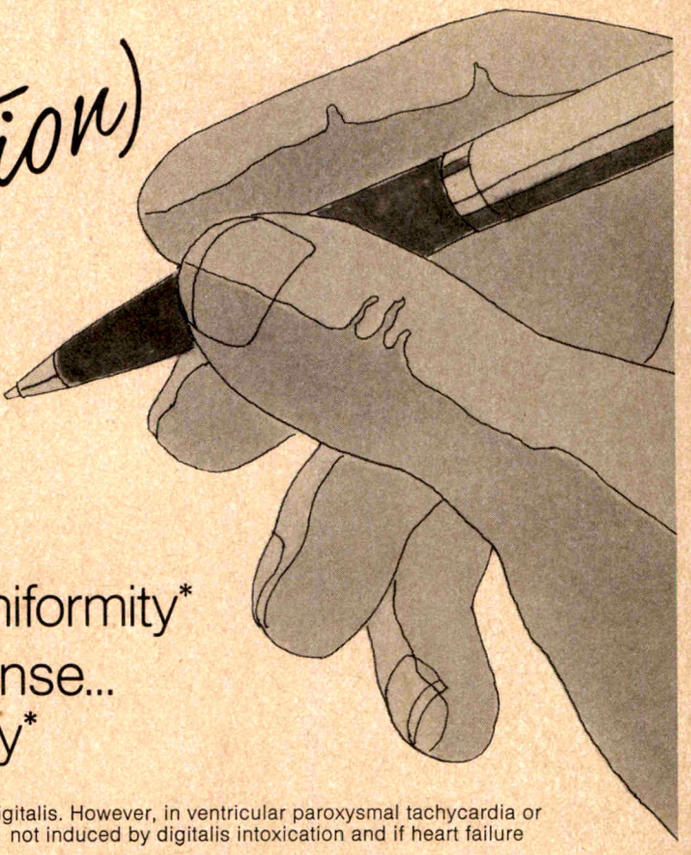
20 ml.
in 30 seconds or less
for direct action

SWW-4940

Schering

Schering Corporation
Kenilworth, N.J. 07033

Lanoxin
[digoxin]
(no substitution)



write it

precision quality control...
- assured tablet content uniformity*

predictable patient response...
- proven biologic availability*

Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

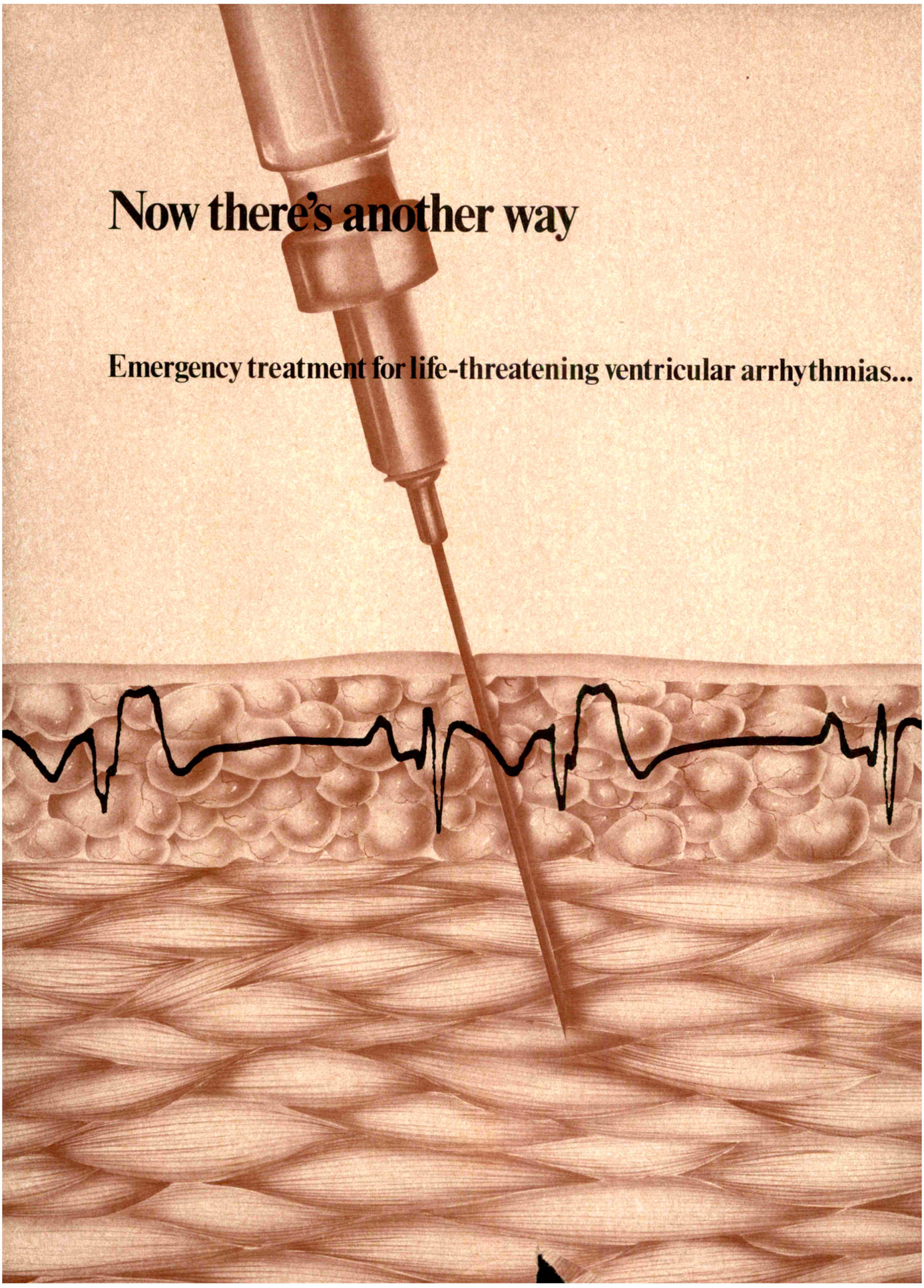
LANOXIN® digoxin TABLETS. **0.125 mg.** (yellow) in bottles of 100 and 1,000. **0.25 mg.** (white) scored, in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack, strips of 10 tablets, 10 boxes of 100 tablets (1,000). **0.5 mg.** (green) scored, in bottles of 100 and 1,000.

Lanoxin® digoxin

*Complete literature available on request from Professional Services Dept. PML.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709


Now there's another way
Emergency treatment for life-threatening ventricular arrhythmias...

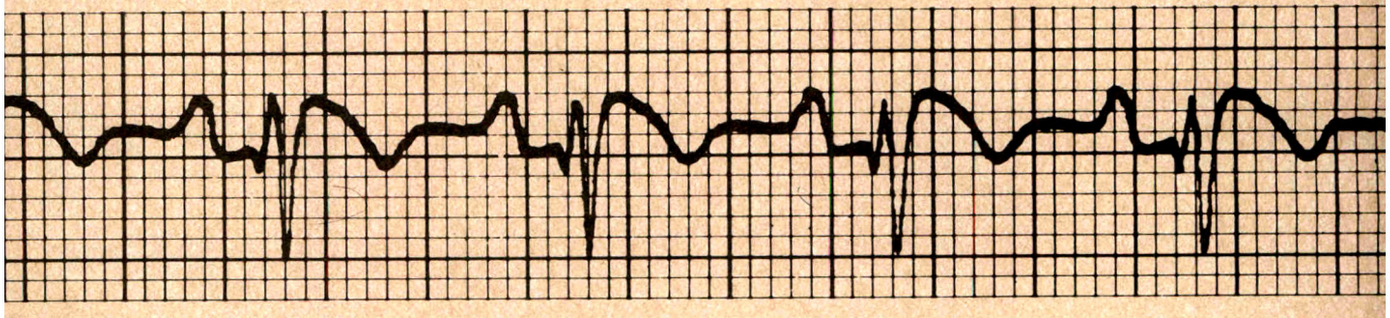
When an appropriate dose of Xylocaine is administered by the intramuscular (deltoid) route, effective antiarrhythmic blood levels are usually attained within 5-15 minutes and may persist for 60-90 minutes. Xylocaine Intramuscular is specifically indicated in the acute management of life-threatening ventricular arrhythmias when justified:

- by a physician when ECG equipment is not available to verify diagnosis, but potential benefits may outweigh possible risks
- by a physician when IV facilities are not available
- by paramedical personnel in a mobile coronary care unit directed by a physician viewing a transmitted ECG

New Xylocaine® (lidocaine) HCl

Intramuscular injection for cardiac arrhythmias

Usual dosage: For the average 150 lb man, 3 ml (300 mg) injected in deltoid muscle. See complete instructions in package insert.



Before prescribing or administering, please consult complete product information, a summary of which follows:

Contraindications: Patients with known hypersensitivity to local anesthetics of the amide type, and patients with Adams-Stokes syndrome or severe degrees of sinoatrial, atrioventricular or intraventricular block.

Warnings: ASPIRATE FREQUENTLY TO AVOID INADVERTENT INTRAVASCULAR ADMINISTRATION.

ECG monitoring is recommended. However, in emergency situations when a physician suspects ventricular arrhythmia and ECG equipment is not available, a single dose may be administered when the physician determines potential benefits outweigh possible risks. If possible, have emergency resuscitative drugs and equipment immediately available to manage potential adverse reactions involving cardiovascular, respiratory, or central nervous systems.

Intramuscular use of Xylocaine® may result in increased creatine phosphokinase levels and compromise the use of this enzyme determination, without isoenzyme separation, in diagnosing acute myocardial infarction.

Pediatric use is not recommended.

Precautions: Observe usual precautions in the presence of impaired renal or hepatic function, hypovolemia and shock, and all forms of heart block.

Adverse Reactions: Although serious adverse reactions to Intramuscular Xylocaine have been rare, the following previously have been reported following lidocaine administration:

1. Central Nervous System—lightheadedness; drowsiness; dizziness; apprehension; euphoria; tinnitus; blurred or double vision; vomiting; sensations of heat, cold, or numbness; twitching; convulsions; unconsciousness; respiratory depression and arrest.
2. Cardiovascular System—hypotension; cardiovascular collapse; bradycardia which may lead to cardiac arrest.

Cross-sensitivity with procainamide or quinidine has not been reported.

Soreness at injection site, occasionally.

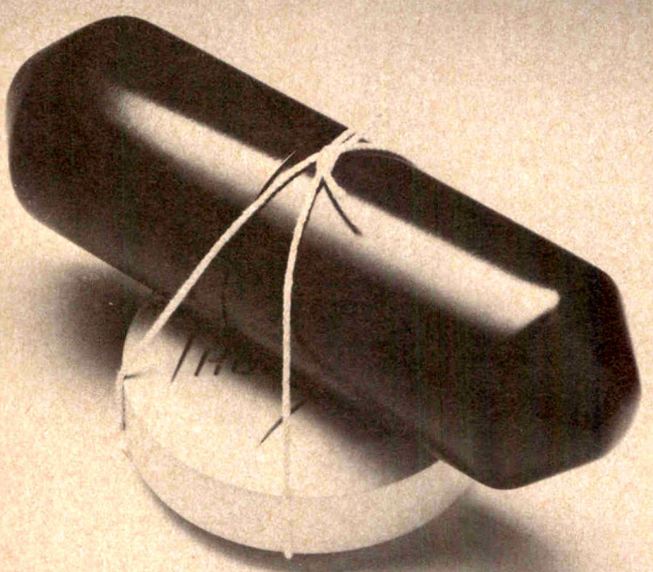
Supplied in 5 ml ampules, in cartons of 10. Each ml contains 100 mg of Xylocaine HCl and sodium hydroxide to adjust pH. A 3 ml injection provides the recommended dose.

FOR INTRAMUSCULAR USE ONLY.

ASTRA®

Astra Pharmaceutical Products, Inc.
Worcester, Massachusetts 01606

Logical partners in control of cardiac edema*



Dyrenium® & Lasix®†

brand of **triamterene** 50 mg. and 100 mg. capsules brand of **furosemide**

To help keep essential K^+ in while getting excess water out

'Dyrenium' exerts its potassium-conserving effect on the first day of administration, despite hyperaldosteronism secondary to furosemide-reduced fluid volume. No need to wait critical days for potassium conservation to begin, no risk of steroid side effects.

When given together, initial dosage of both agents should be reduced. 'Lasix' is a potent diuretic, and 'Dyrenium' has an additive effect, so careful supervision and dosage adjustment is required. K^+ supplements should not be given unless dosage adjustment fails to reduce excessive potassium loss, hypokalemia develops, or dietary intake of K^+ is markedly reduced. Hyperkalemia can occur, but it is rare in patients with normal renal function. The elderly, diabetics, or patients with suspected or confirmed renal insufficiency should be observed closely; check serum K^+, BUN, and CO_2 periodically.

†**'Lasix' is contraindicated in women of child-bearing potential, anuria, increasing azotemia and oliguria, hepatic coma or electrolyte depletion, hypersensitivity to the drug, and pediatric patients. Initiation of therapy in patients with hepatic cirrhosis and ascites is best carried out in the hospital. Before prescribing, see complete prescribing information in Hoechst-Roussel literature or *PDR*.**

See facing page for 'Dyrenium' indications and brief summary of prescribing information.

Dyrenium®

brand of **triamterene**

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

***Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid induced edema, idiopathic edema, edema due to secondary hyperaldosteronism and edema resistant to other diuretic therapy.**

Contraindications: Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

Dyrenium (triamterene, SK&F) and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.
Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 50 and 100 mg. capsules, in bottles of 100 and in Single Unit Packages of 100 (intended for institutional use only).

SK&F Co., Carolina, P.R. 00630
Subsidiary of SmithKline Corporation

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ABC

Principles of oral anticoagulation

Practical Considerations

Identifying your patient at risk of thromboembolic complications

While every MI patient is not a candidate for oral anticoagulation therapy, a history of previous infarct or angina, persistent atrial fibrillation or congestive failure, severe hypotension or shock or serious arrhythmia may increase risk of thromboembolic complications.

In addition, certain procedures often place your surgical patient, particularly if he's over 40 years of age, in the high risk category—cup arthroplasty or pelvic surgery, heart valve replacement, reparative vascular surgery.

Your geriatric patient, too, is at high risk of thromboembolism if he's suffered a fracture—especially of the hip, pelvis or a lower extremity—or if his history includes venous insufficiency.

For any of these individuals, obesity, previous episodes of venous thrombosis or pulmonary embolism and a future including prolonged bed rest all increase the risk of thromboembolic complications, and make him a candidate for oral anticoagulation.

Laboratory monitoring

For every patient receiving COUMADIN® (*crystalline* sodium warfarin), frequent laboratory monitoring is a key to effective therapy. Determine prothrombin time daily until results stabilize in the therapeutic range —1½ to 2½ times normal. Individualize dosage and administration as indicated by prothrombin time results. Determine subsequent prothrombin times periodically throughout the course of therapy.

Educating your patient

Because a patient is generally more reliable if he understands his condition and his medication, he should be made aware of the factors that may influence his prothrombin time and, therefore, his response to COUMADIN®—dietary change, travel, other medication, change in physical condition and abrupt environmental change. What's more, he should know the importance of regularly taking the exact dosage of COUMADIN® prescribed and of keeping every appointment with you and with the laboratory.

COUMADIN® is an Endo U.S. registered trademark.

Therapeutic principles put into practice

COUMADIN®

CRYSTALLINE SODIUM WARFARIN*)

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional and lumbar block anesthesia.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Pregnancy–COUMADIN® passes through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage **in utero,** even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. The newborn may be particularly sensitive to sodium warfarin. There have been reports of birth malformations in children born to mothers who have been treated with warfarin during the first trimester of pregnancy. Whether warfarin was in fact the responsible agent has not been established. Therefore, women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed. If COUMADIN® must be used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks. **Lactation**–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Spinal puncture. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN®.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methylphenidate; monoamine oxidase inhibitors; nalidixic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates (in excess of 1 Gm/day); sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K-dependent factors, namely Factors VII, IX, X and II, the factors affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN® may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time; and therefore, when patients are receiving both heparin and COUMADIN®, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN® may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Water for Injection. 75 mg: Unit consists of 1 vial, 75 mg; sodium chloride, 15 mg; thimerosal, 0.3 mg. pH is adjusted with sodium hydroxide, accompanied by a 3 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

Rev. April, 1975

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

EDO-2620

DUPONT

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The Roche Mobile Computerized ECG Station contains its own minicomputer, recorder, and printer. It can eliminate the routine work associated with the reading of normal ECG's. It is highly accurate, classifying correctly 95-98% of normal ECG's, 85% of abnormals.[1] It is fast, supplying a computer printout based on the widely accepted USPHS program within a minute after readings are taken.

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The Roche Mobile Station offers considerable savings over telephone tie-in ECG systems and yet avoids the extensive investment required for a dedicated central computer. Economic feasibility studies and additional information are available from Roche.

1. Hochberg, H. M., et al.: Automatic electrocardiogram analysis in rapid mass screening. *Arch. Environ. Health* 15:390-398, 1967.

For more information

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☐ Please have representative call.

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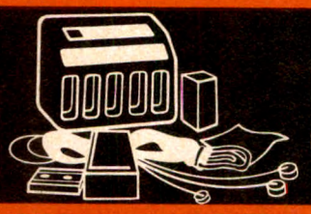

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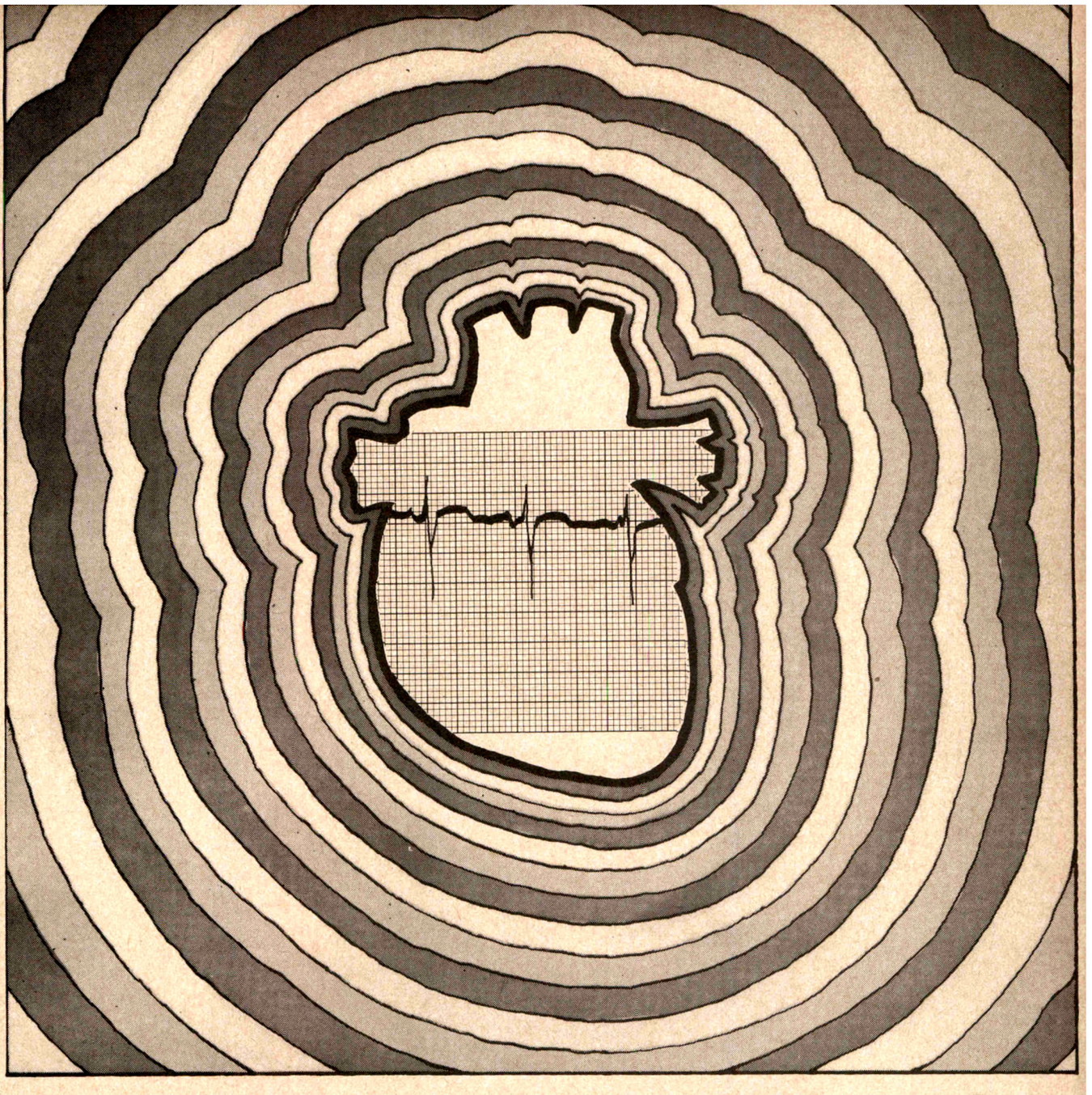

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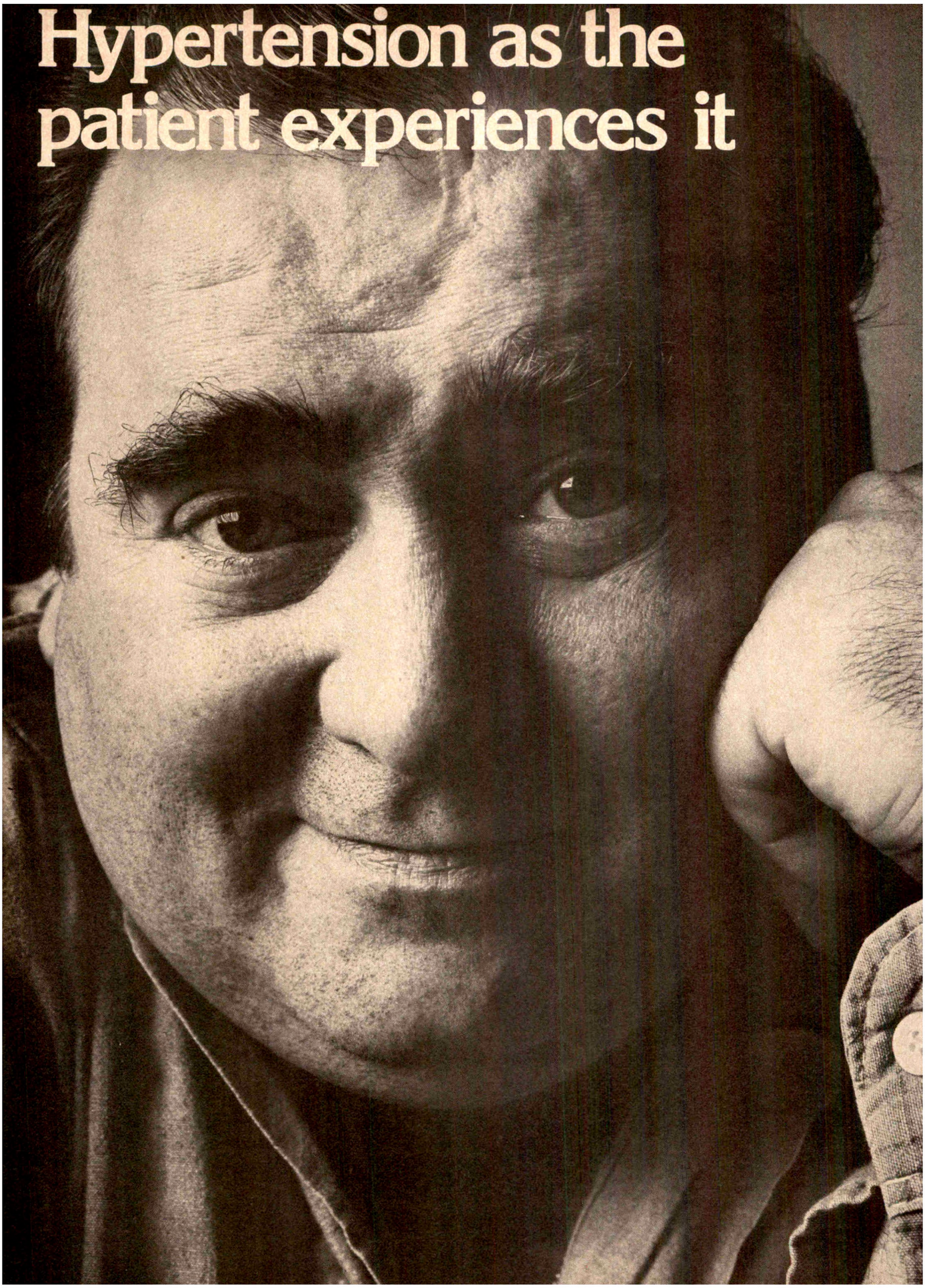
Hypertension as the patient experiences it



What you hear.

"Hard to believe, doctor. Me... Industrial League softball pitcher of the year ...with high blood pressure.

High blood pressure sure is a pain in the neck. We must have tried half-a-dozen different water pills and a lot of other stuff. Some of 'em worked for a while.

But looks like we really might have a handle on it this time. You tell me this one has my blood pressure down around where it should be, and it's keepin' it there. That's great.

And I only have to take this one once a day. I like that. You know me... always on the go.

I feel great these days, and I don't seem to have any problems with this one."

What the investigators say.

"The present study clearly establishes that at a dose of 2.5 mg. per day, metolazone [Zaroxolyn] is an effective hypotensive drug, lowering blood pressure approximately 25/15 mm. Hg."[1]

"The high frequency of **good** to **excellent** response, once a day administration, potentiation of other nondiuretic antihypertensive agents, and the failure of tolerance to develop in long-term use would seem to be the major advantages of metolazone [Zaroxolyn]."[2]

"Metolazone [Zaroxolyn] was remarkably well tolerated. In no patient was the drug discontinued because of side effects."[3*]

*In a larger population the incidence of discontinuation of therapy due to adverse side effects was 8/188 or 4.3%. Data on file, Medical Department, Pennwalt Prescription Products.

Zaroxolyn®
Metolazone, PENNWALT

Antihypertensive diuretic

Please see following page for brief summary of prescribing information.

Zaroxolyn®
Metolazone, PENNWALT

It's convenient and comfortable for hypertensive patients

2½ 2½ mg 5 5 mg 10 mg 10

Recommended Dosages Zaroxolyn® (metolazone)

Mild to moderate essential hypertension	2½ to 5 mg once daily
Edema of cardiac failure	5 to 10 mg once daily
Edema of renal disease	5 to 20 mg once daily

NOTE: The daily dosage depends on the severity of each patient's condition, his sodium intake, and his responsiveness. Therefore, dosage adjustment is usually necessary during the course of therapy.

Prescribing Information: Zaroxolyn®

NB: For patients with congestive cardiac failure who tend to experience paroxysmal nocturnal dyspnea, it is usually advisable to employ a dosage near the upper end of the range, to ensure diuresis and saluresis for a full 24-hour period.

Once desired therapeutic effect has been achieved, it is usually desirable to reduce daily dosage to a lower maintenance level.

INDICATIONS: ZAROXOLYN (Metolazone) is indicated for the treatment of edema accompanying congestive heart failure and renal disease, and to reduce blood pressure in the management of mild to moderate essential hypertension.

CONTRAINDICATIONS: Anuria. Hepatic coma or pre-coma; Allergy or hypersensitivity to ZAROXOLYN.

The routine use of diuretics in an otherwise healthy pregnant woman, with or without mild edema, is contraindicated and possibly hazardous.

WARNINGS: While not reported to date, cross-allergy theoretically may occur when ZAROXOLYN is given to patients known to be allergic to sulfonamide-derived drugs, thiazides, or quinethazone.

Hypokalemia may occur, with consequent weakness, cramps, and cardiac dysrhythmias. It is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may be precipitated.

Azotemia and hyperuricemia may be noted or precipitated during the administration of ZAROXOLYN. Infrequently, gouty attacks have been reported in persons with history of gout. Discontinue ZAROXOLYN if azotemia and oliguria worsen during treatment of patients with severe renal disease.

Presently, ZAROXOLYN is not recommended for pediatric patients.

ZAROXOLYN will, on occasion, exhibit considerable potentiation when administered concurrently with furosemide. Excessive, massive volume and electrolyte depletion may result. Exert care, especially during initial therapy, when using ZAROXOLYN with other antihypertensives. Dosage of other antihypertensive agents, especially the ganglionic blockers, should be reduced.

Use of ZAROXOLYN with a potassium-sparing diuretic may potentiate diuresis; dosage should be reduced. Potassium retention and hyperkalemia may result; serum potassium should be determined frequently. Potassium supplementation is contraindicated when a potassium-sparing diuretic is given.

USAGE IN PREGNANCY (See Contraindications): Since ZAROXOLYN crosses the placenta, and appears in the cord blood, its administration to women of child bearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. The potential effects on the fetus include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

NURSING MOTHERS: ZAROXOLYN appears in breast milk. Thus it is possible that the effects of ZAROXOLYN may occur in the newborn. If the use of ZAROXOLYN is deemed essential for a nursing mother, the patient should stop nursing.

PRECAUTIONS: Periodic assessment of serum electrolytes, blood urea nitrogen, uric acid, and glucose levels should be made at intervals during therapy.

Patients receiving ZAROXOLYN therapy should be observed for clinical signs of fluid and/or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Serum potassium should be determined regularly, and potassium supplementation instituted as indicated. Hypokalemia will be more common in association with intensive or prolonged diuretic therapy, with concomitant steroid or ACTH therapy, and with inadequate electrolyte intake.

While not reported to date for ZAROXOLYN, related diuretics have increased responsiveness to tubocurarine and decreased arterial responsiveness to norepinephrine. Accordingly, it may be advisable to discontinue ZAROXOLYN three days before elective surgery.

Observe caution when administering ZAROXOLYN to hyperuricemic or gouty patients. ZAROXOLYN exerts minimal affects on glucose metabolism; insulin requirements may be affected in diabetics, and hyperglycemia and glycosuria may occur in patients with latent diabetes.

Chloride deficit and hypochloremic alkalosis may occur. In patients with severe edema accompanying cardiac failure or renal disease, a low-salt syndrome may be produced; hot weather and a low-salt diet will contribute.

Observe caution when administering ZAROXOLYN to patients with severely impaired renal function. As most of the drug is excreted by the renal route, cumulative effects may be seen in this circumstance.

Orthostatic hypotension may occur; this may be potentiated by alcohol, barbiturates, narcotics, or concurrent therapy with other antihypertensive drugs.

While not reported for ZAROXOLYN, use of other diuretics has been associated on rare occasions with pathological changes in the parathyroid glands, with hypercalcemia and hypophosphatemia.

ADVERSE REACTIONS: *Gastrointestinal reactions:* Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis. *Central nervous system reactions:* syncope, dizziness, drowsiness, vertigo, headache. *Cardiovascular reactions:* orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation and chest pain. *Hematologic:* leukopenia, *Dermatologic-hypersensitivity:* urticaria and other skin rashes. *Other reactions:* dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine; fatigue, muscle cramps or spasm, weakness, restlessness, chills and acute gouty attacks.

Adverse reactions which occur with other diuretics, but have not been reported to date for ZAROXOLYN include: pancreatitis, paresthesias, xanthopsia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity and necrotizing angiitis (cutaneous vasculitis). These reactions should be considered as possible occurrences with clinical usage of ZAROXOLYN.

Whenever adverse reactions are moderate or severe, dosage should be reduced or therapy withdrawn.

HOW SUPPLIED: Tablets, 2½, 5 and 10 mg.

1. Pilewski RM, et al: Techniques of controlled drug assay in hypertension. V. Comparison of hydrochlorothiazide with a new quinethazone diuretic, metolazone. *Clin Pharmacol Ther* **12:**5, 1971.
2. Cangiano JL, et al: The effects of metolazone in the long-term treatment of essential hypertension. *Curr Ther Res* **16:**8, 1974.
3. Materson BJ, et al: Antihypertensive effects of metolazone (Zaroxolyn). *Curr Ther Res* **16:**9, 1974.

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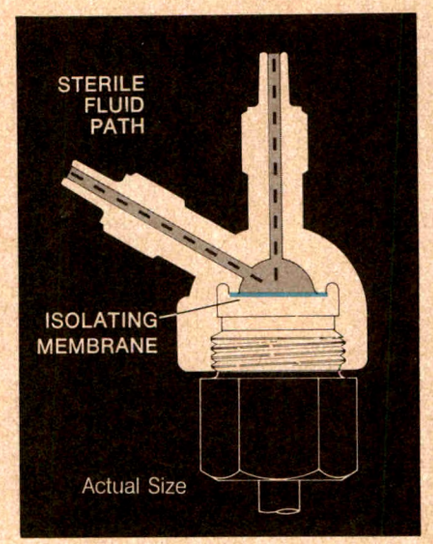

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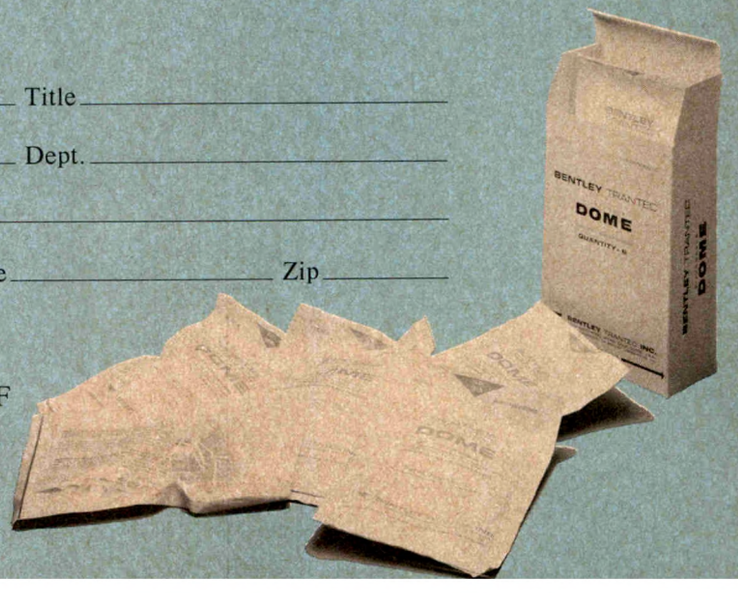

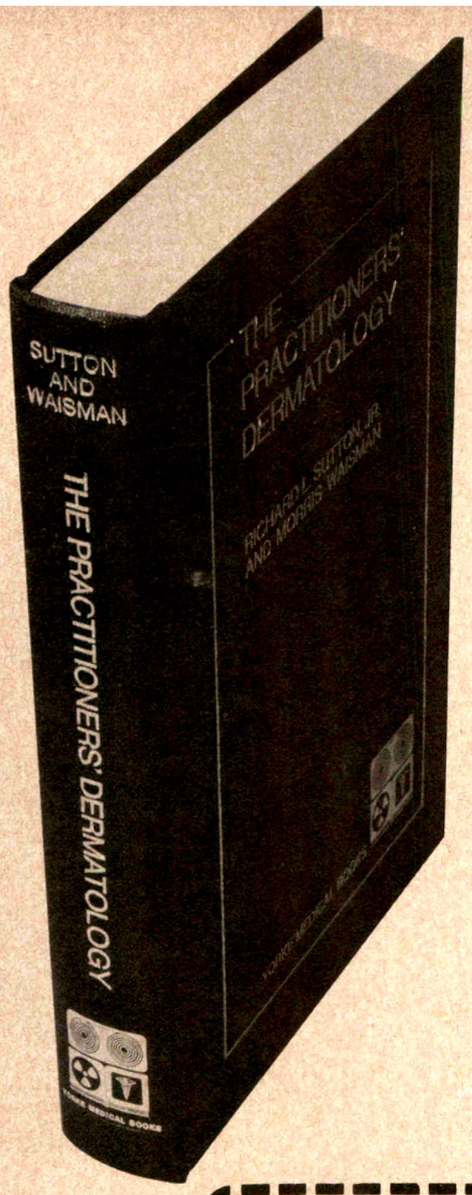

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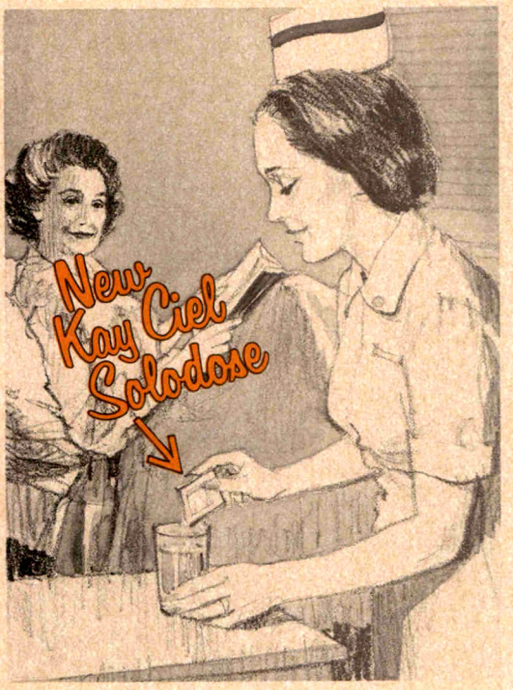

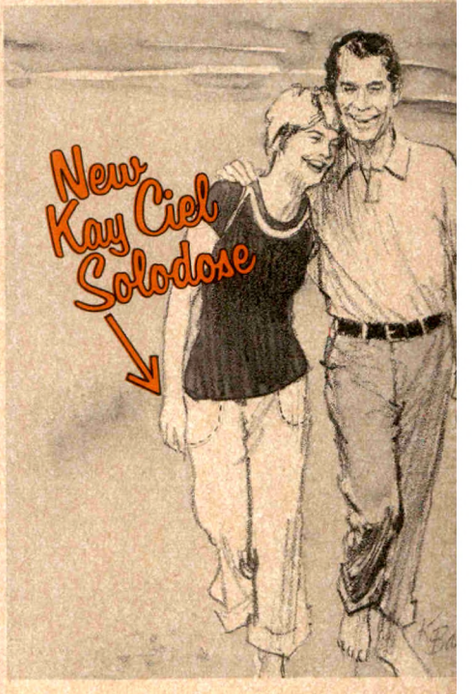

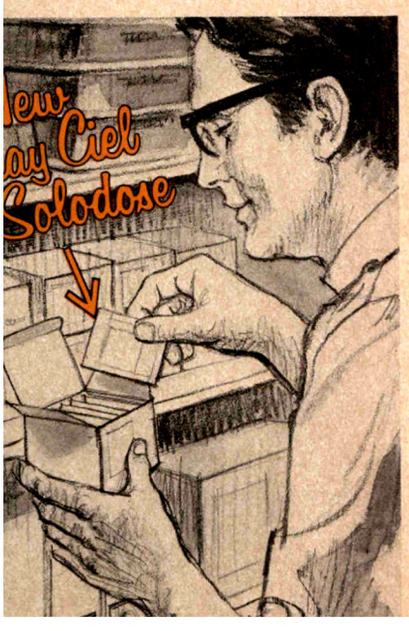

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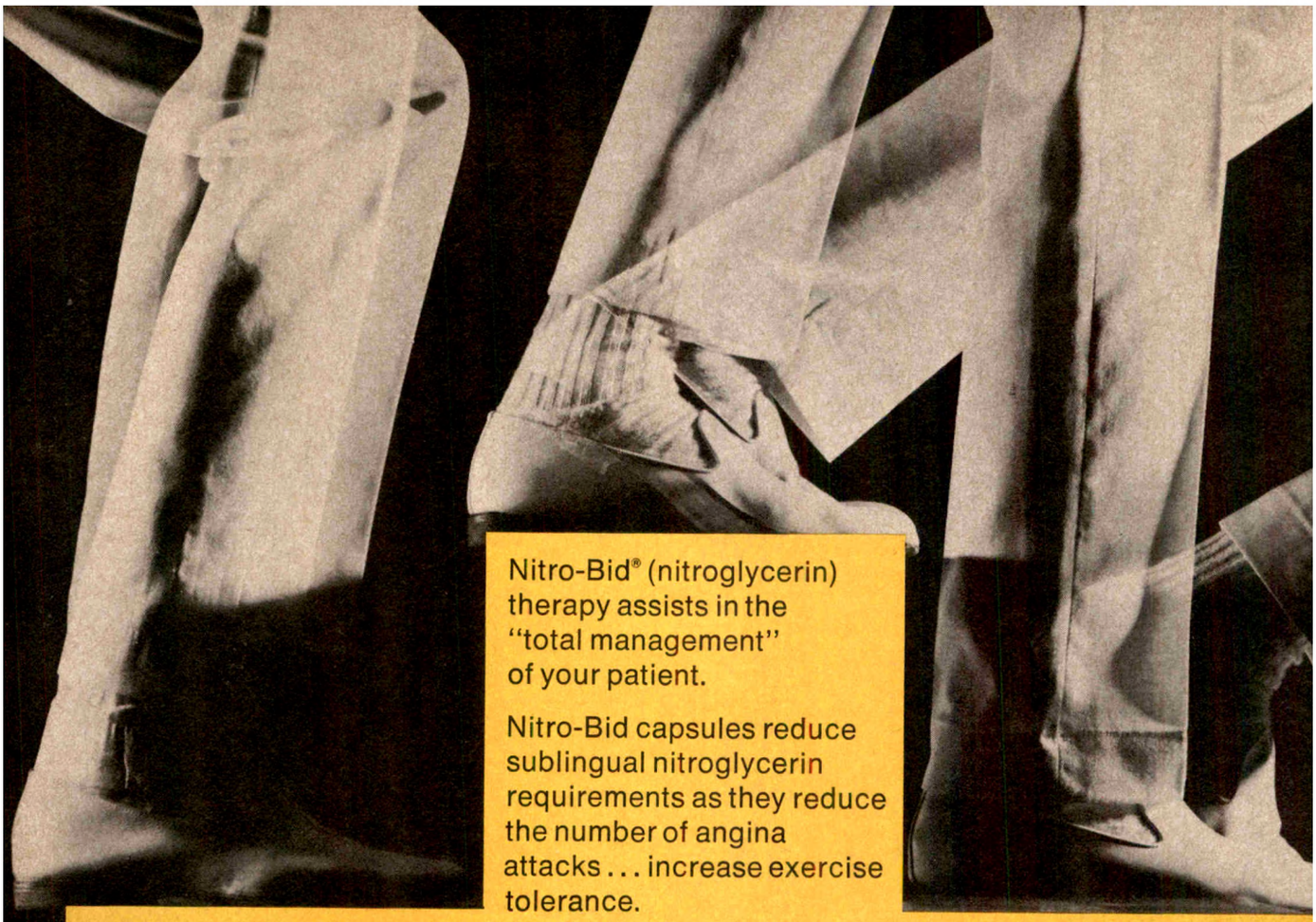

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Reference: 1. Master, AM: The management of angina pectoris. *Modern Medicine* **38**:92-100 (Feb 23) 1970.

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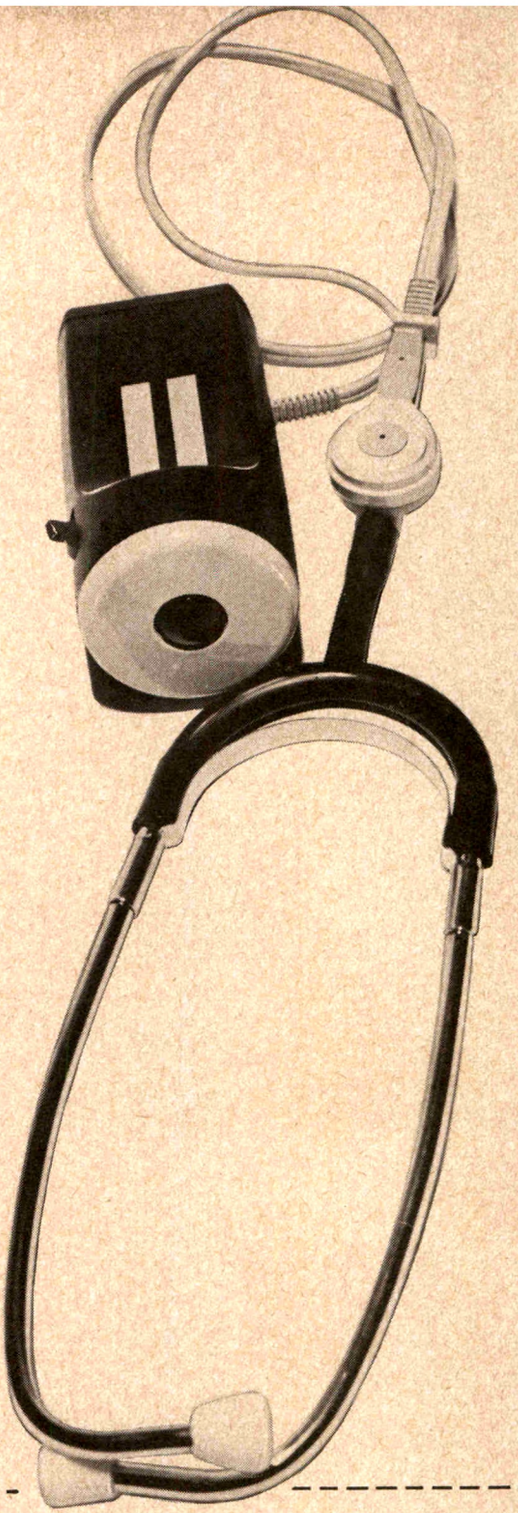

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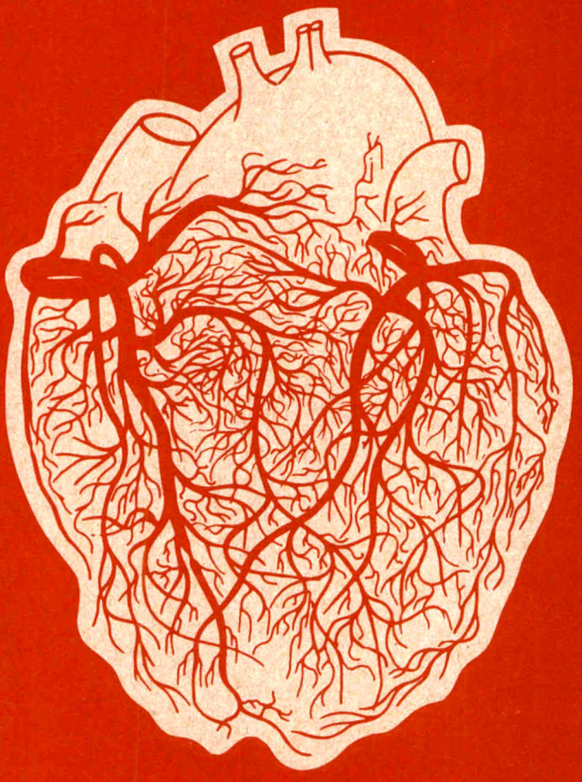

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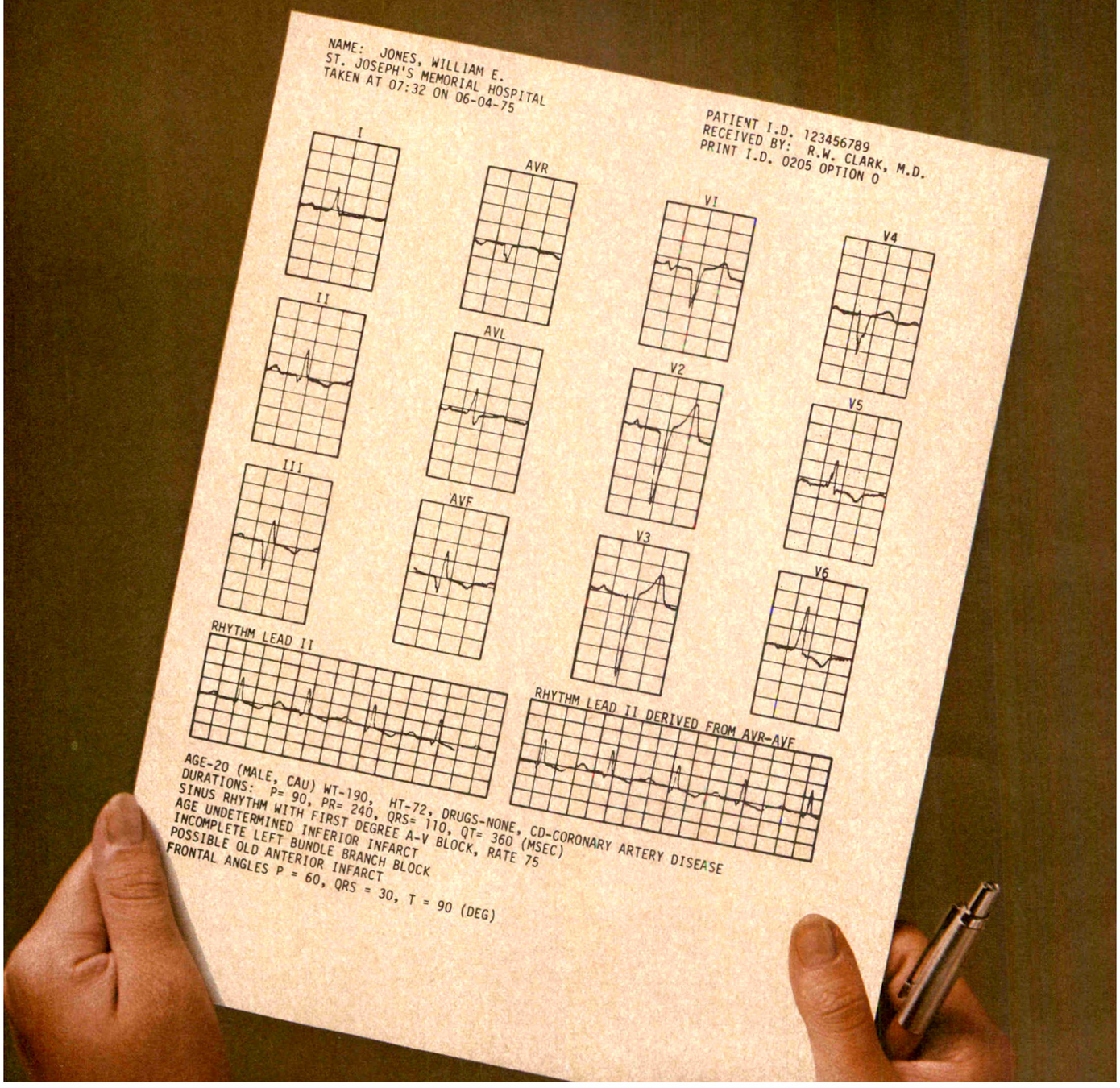

The American Journal of CARDIOLOGY®

VOLUME 36

NUMBER 4

CLINICAL STUDIES

Regional Left Ventricular Wall Dynamics Before and After Sublingual Administration of Nitroglycerin

JEAN G. DUMESNIL, MD
ERIK L. RITMAN, MB, PhD
GEORGE D. DAVIS, MD
GERALD T. GAU, MD, FACC
BARRY D. RUTHERFORD, MB, FRACP
ROBERT L. FRYE, MD, FACC

Rochester, Minnesota

Regional wall dynamics of the left ventricle before and after sublingual administration of 0.6 mg of nitroglycerin were determined from left ventricular angiograms in 27 patients undergoing coronary arteriography. Regional wall dynamics were quantitatively measured from 60/sec determinations of wall thickness and derived peak rate of systolic wall thickening (peak dTw/dt) in selected sites of the left ventricle. A total of 70 regions were studied. Analysis of the same segment before and after administration of nitroglycerin revealed that the mean change in peak dTw/dt was +1.97 cm/sec in segments with an initial peak dTw/dt of less than 5 cm/sec, in contrast to a change of +0.66 cm/sec in segments with an initial control value of 5 cm/sec or greater. Akinetic or dyskinetic areas did not show improvement after nitroglycerin. In 11 left ventriculograms, an area that was initially hypokinetic manifested an increase in rate of wall thickening after nitroglycerin. The mean increase in peak dTw/dt in anterior segments with electrocardiographic evidence of myocardial infarction was 0.18 cm/sec ($P < 0.05$) after nitroglycerin, compared with a mean change of 1.33 cm/sec in anterior segments without such evidence. This study presents evidence for a regional myocardial response to nitroglycerin with differing responses within the same ventricle apparently depending upon the functional state of the underlying myocardium.

The hemodynamic and metabolic effects of nitroglycerin in patients with coronary artery disease have been documented by many observers.[1–3] Studies of the effects of nitroglycerin on total as well as regional myocardial blood flow[4–6] indicate that sublingual administration of the drug has a systemic effect on the peripheral circulation and alters the distribution of myocardial blood flow. The relative importance of each mechanism in explaining the beneficial effect in relief of angina pectoris remains controversial and little is known about the specific effect of nitroglycerin on the regional patterns of contraction of the left ventricle. The latter is of interest since in patients with coronary artery disease the underlying functional state of the myocardium may differ from one ventricular area to another. This study was designed

From the Mayo Clinic and Mayo Foundation, Rochester, Minn. This investigation was supported in part by Research Grants HL-14196F, RR-7, and HL-4664 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md. Manuscript accepted March 19, 1975.

Address for reprints: Erik L. Ritman, MB, Department of Physiology, Mayo Clinic, Rochester, Minn. 55901.

TABLE I

Clinical, Coronary Angiographic and Hemodynamic Data in Control State (C) and After Administration of Nitroglycerin (NTG)

Case no.	Age (yr) & Sex	ECG Diagnosis	Degree of Stenosis*			LVSP (mm Hg)		LVEDP (mm Hg)		EDV (ml)		EF (%)		SW (g-m)		Region Studied	Peak dTw/dt (cm/sec)	
			LAD	LCx	RCA	C	NTG	C	NTG	C	NTG	C	NTG	C	NTG		C	NTG
Group I: Patients with Coronary Artery Disease																		
1	52M	Inf-apical infarct	3	0	4	158	NA‡	9	NA	170	97	62	72	NA	NA	Mid ant Post-lat	3.96 8.96	4.48 9.24
2	51M	Inf infarct	3	4	4	136	NA	24	NA	173	192	40	59	NA	NA	Mid ant Low ant Post-lat (I)	7.2 2.4 1.52	8.8 6.4 4.64
3	51M	Normal	0	3	0	124	107	28	17	108	86	69	76	100.2	79.8	Mid ant Post-lat	6.30 3.50	6.16 5.80
4	50M	Inf infarct	4	4	3	128	117	41	34	187	141	55	50	146.8	91.7	Mid ant Post-lat (I)	2.10 1.33	4.06 1.26
5	41M	Low ant force	4	3	0	127	128	13	14	172	163	51	49	112.8	103.7	Mid ant Post-lat	4.06 2.94	7.00 4.77
6	61M	Ant-lat inf infarct	4	2	4	144	NA	41	NA	246	235	21	25	NA	NA	Mid ant (I) Post-lat Post-lat (I)	0 2.24 0	0 5.04 0
7	48M	Low ant force	4	3	0	117	116	14	11	102	90	57	72	67.7	65.1	Mid ant Low ant	7.7 2.8	8.4 4.76
8	63M	Inf-apical infarct	3	3	4	146	143	18	19	136	115	57	75	112.3	109.1	Mid ant Low ant Post-lat	4.06 1.82 1.68	7.74 6.30 3.36
9	47M	Ant-sept infarct	4	2	4	122	96	11	8	180	108	28	39	62.9	41.8	Mid ant (I) Low ant (I) Post-lat Post-apical (I)	3.25 1.24 5.52 3.2	3.25 2.08 5.0 1.82
10	60M	Post infarct	2	4	4	115	147	27	17	132	101	66	73	160.9	105.5	Mid ant Post-lat (I)	5.46 1.47	5.46 3.01
11	41M	Inf infarct	2	3	4	164	145	25	25	118	114	51	57	103.6	101.7	Mid ant Low ant Post-lat (I)	2.94 2.52 2.24	6.16 6.58 7.7
12	47M	Normal	1	4	4	129	110	13	7	96	96	57	56	70.5	66.5	Mid ant Post-lat	8.40 2.03	8.82 2.24
13	54M	LBBB	4	1	4	124	127	14	16	109	94	34	43	NA	NA	Mid ant Low ant Post-lat	0.56 0.7 4.76	1.75 1.47 5.6
14	47M	Normal	0	4	0	95	79	15	10	124	84	60	78	75.6	55.1	High ant Mid ant Low ant Post-lat	4.31 3.95 3.78 2.94	6.21 5.75 5.75 6.02
15	66M	ST-T wave changes	2	3	2	185	145	17	7	82	61	60	60	82.5	46.7	High ant Low ant Post-lat	4.76 4.33 5.0	6.17 6.02 5.44
16	45M	ST-T wave changes	3	3	1	142	145	11	19	84	80	50	59	61.1	73.1	Mid ant Post-lat	6.56 3.2	6.08 4.98
17	56M	Ant-lat infarct	3	3	3	124	123	32	20	155	147	28	30	58.3	58.9	High ant (I) Low ant (I) Post-lat	1.71 <0 0.82	1.87 <0 0.75

18	47M	Ant-sept, lat infarct	3	3	1	106	107	18	16	118	109	43	55	55.8	65.6	Mid ant (I) Low ant (I) Post-lat	0.63 1.40 2.59	1.33 1.33 6.3
19	51M	ST-T wave changes	4	4	2	125	107	23	19	131	74	53	44	90.7	38.9	High ant Low ant Post-lat	2.94 7.2 0	3.64 6.16 0
20	64M	Ant-sept infarct	3	2	0	101	97	29	22	152	152	33	40	56.9	62.2	Mid ant (I) Post-lat	<0 3.36	<0 6.02
21	51M	Inf infarct	3	3	5	168	140	20	15	132	133	44	44	98.5	80.2	Mid ant Low ant Post-lat (I)	2.7 2.1 0	4.5 2.1 0
Mean						133	121	20	16	138	118	48	55	89.2	73.3			
SD						±25	±20	±8	±7	±39	±42	±13	±15	±31.2	±22.6			
P value							<0.001		<0.01		<0.001		<0.001		<0.01			
Group II: Patients with Normal Coronary Arteries																		
22	44F	Normal	0	0	0	163	154	16	17	90	74	48	64	68.7	75.8	Mid ant Post-lat	5.4 5.1	5.7 6.0
23	28M	Normal	0	0	0	103	96	14	11	85	76	51	60	47.4	44.0	Mid ant Post-lat	6.2 5.6	5.6 5.5

*Degree of stenosis by coronary arteriogram: 0 = normal; 1 = less than 50 percent luminal narrowing; 2 = less than 75 percent luminal narrowing; 3 = 75 percent luminal narrowing; 4 = complete occlusion.

Ant = anterior; dTw/dt = rate of wall thickening during systole; ECG = electrocardiographic; EDV = end-diastolic volume; EF = ejection fraction; (I) = considered the infarcted segment; Inf = inferior; LAD = left anterior descending coronary artery; Lat = lateral; LBBB = left bundle branch block; LCx = left circumflex coronary artery; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; NA = not available; *P* = probability; Post = posterior; RCA = right coronary artery; SD = standard deviation; Sept = septal; SW = stroke work.

to test the reversibility of abnormal segmental left ventricular function in patients with coronary artery disease after the sublingual administration of nitroglycerin. Regional wall dynamics were quantitatively evaluated by means of roentgen videometry for 60/sec determinations of wall thickness in selected sites of the left ventricle, as recently described.[7]

Methods

Case material: Twenty-seven patients who underwent selective coronary arteriography were studied. The procedure was performed in 24 patients for definition of coronary anatomy in consideration of surgery to relieve angina pectoris and in 3 patients for diagnostic evaluation of unexplained chest pain. None of the patients had clinical evidence of congestive heart failure or cardiomegaly. Results were studied in three groups of patients: Group I, 21 patients with coronary artery disease who were given nitroglycerin; Group II, 2 patients with normal coronary arteries who were given nitroglycerin; and Group III, 4 patients with two left ventriculographic studies who received no nitroglycerin before the second study. Clinical and laboratory data for the 23 patients in Groups I and II are listed in Table I. Cardiac catheterization was performed with the patient in the fasting state after the intramuscular administration of sodium pentobarbital, 100 mg. Left heart catheterization and left ventriculography were performed retrograde from the right brachial artery, and coronary arteriograms were obtained by the Sones technique.

Procedures: The studies of the effect of nitroglycerin on regional left ventricular wall dynamics were made before coronary arteriography. Resting hemodynamic measurements were first recorded, and the patient was then placed in the right anterior oblique position. All left ventriculograms were obtained with a General Electric Fluoricon 300 biplane X-ray system. The control left ventriculogram was obtained with continuous injection of 50 ml of Renografin® through a no. 7 National Institutes of Health catheter over 3 to 4 seconds while the patient maintained a deep inspiration. Seven minutes after the control left ventriculograms, hemodynamic data were recorded with the patient in the same position and 0.6 mg of nitroglycerin was administered sublingually. Three minutes after administration of nitroglycerin, hemodynamic data were recorded and a second left ventriculogram was performed in exactly the same manner. In four patients, two ventriculograms obtained 5 to 10 minutes apart without an intervention were available for study. These were the result of the need to repeat the left ventriculogram because of a problem in positioning of the patient or poor contrast, unrelated to the present study. The biplane video images were recorded as a single split image on 2 inch video tape (rate 60 video fields/sec), as previously described.[8] Simultaneous electrocardiogram and pressure signals were recorded on the same video tape by use of a specially developed video pulse-height modulator system.[9] Reported pressure values are from tracings recorded immediately before the injections of Renografin, with normal respiration.

Left ventricular stroke work was calculated according to the formula stroke work = (VSM − VED) × SV × 0.0144, where VSM represents ventricular mean systolic pressure, VED represents ventricular end-diastolic pressure, SV represents stroke volume and 0.0144 is a conversion constant. The mean ventricular systolic pressure was obtained by planimetric integration.

Left ventriculograms were analyzed with the use of roentgen videometry, which permits determinations at a rate of 60 images per second of left ventricular volume and wall thickness.[7,8] Wall thickness at selected sites was computed as the least distance between the epicardial and endocardial surfaces outlined by the videometric border recognition and measurement system. One value for wall thickness was obtained for each 60/sec video field image recorded during several cardiac cycles of the left ventriculogram. Regional wall dynamics were quantitatively evaluated from computer-generated plots of these 60/sec wall thickness determinations. Measurements performed included end-diastolic wall thickness, mean and peak systolic rates of wall thickening (mean and peak dTw/dt) and fractional increase in wall thickness. Depending on the dimensions of the cardiac silhouette and on the extent over which the epicardium can be satisfactorily identified, one to three sections of the anterior wall and one to two sections of the posterolateral wall can generally be studied.

Electrocardiograms were independently interpreted by two of us (J.G.D. and G.T.G.) without knowledge of the immediate results of the videometric analysis. Patients classified as having myocardial infarction had unequivocal electrocardiographic and vectorcardiographic evidence of transmural myocardial infarction. Patients with questionable electrocardiographic evidence of infarction, such as anterior infarction in the presence of left bundle branch block, were not classified as having evidence of myocardial infarction.

Results

Group I—patients with coronary artery disease and nitroglycerin studies: In the 21 patients of this group, the luminal diameter of one or more major coronary arteries was diminished by more than 75 percent. The hemodynamic changes in this group are listed in Table I. After the administration of nitroglycerin, mean left ventricular systolic pressure (mm Hg) decreased from 133 ± 25 (standard deviation) to 121 ± 20 (P <0.001) and mean left ventricular end-diastolic pressure (mm Hg) decreased from 20 ± 8 to 16 ± 7 (P <0.01). Left ventricular end-diastolic volume (ml) was decreased by 16 percent, from 138 ± 39 to 118 ± 42 (P <0.001), and the ejection fraction (percent) was increased from 48 ± 13 to 55 ± 15 (P <0.001). Left ventricular stroke work (g-m) decreased from 89.2 ± 31.2 to 73.3 ± 22.6 (P <0.01).

A previous study of this method[8] revealed that peak rate of systolic wall thickening (dTw/dt) is the variable that is most sensitive to changes in wall dynamics. Regional dynamics are classified as normal (peak dTw/dt greater than 5 cm/sec), hypokinetic (peak dtW/dt less than 5 cm/sec), akinetic (peak dTw/dt equal to 0) or dyskinetic (peak systolic dTw/dt less than 0).

In the 21 control left ventriculograms from patients with coronary artery disease, 46 segments (28 anterior and 18 posterolateral wall) of the left ventricle had peak dTw/dt values of less than 5 cm/sec and 10 segments (7 anterior and 3 posterolateral wall) had values of more than 5 cm/sec. Analysis of the same segments after administration of nitroglycerin revealed that peak dTw/dt in the 46 segments with an initial value of less than 5 cm/sec changed from −1.4 to +5.5 cm/sec (mean +1.97, standard deviation 1.13, standard error 0.28), compared with a change of −1.0 to +1.6 cm/sec (mean +0.66, standard deviation 46, standard error 0.12) in the segments with control values equal to or greater than 5 cm/sec. There was a statistically greater responsiveness (P <0.01) to nitroglycerin in segments with peak dTw/dt control values of 2 to 5 cm/sec (Fig. 1). Eighteen segments with initial values for peak dTw/dt of less than 5 cm/sec were in the normal range for peak dTw/dt after administration of nitroglycerin (Fig. 1). When segments with a peak dTw/dt of less than 5 cm/sec were classified according to hypokinesis (peak dTw/dt less than 5 but more than 0 cm/sec), akinesis (peak dTw/dt equal to 0) or dyskinesis (peak dTw/dt less than 0), the following difference was noted: No akinetic or dyskinetic area manifested a positive peak dTw/dt after administration of nitroglycerin in spite of a decrease in left ventricular systolic and end-diastolic pressures or a decrease in left ventricular end-diastolic volume, or both.

Of particular interest were left ventriculograms in which peak dTw/dt varied within the same ventricle. In 11 left ventriculograms, an initially hypokinetic area had an increase in rate of wall thickening after administration of nitroglycerin, whereas other regions in the same ventricle did not change. In one case (Fig. 2), a previously hypokinetic region became normal after administration of nitroglycerin, whereas there was little or no change in a region with originally normal dynamics. In another case (Fig. 3), one of two hypokinetic regions within the same ventricle showed greatly improved dynamics after administration of nitroglycerin and the other did not.

Differences in response to nitroglycerin of segments with and without electrocardiographic evidence of myocardial infarction were compared. The mean and standard deviation for the change observed in peak dTw/dt after nitroglycerin in 16 anterior segments without infarction were 1.33 and 1.20, respectively. In five anterior segments with infarction, these values were 0.18 and 0.30, respectively. The differences of these means were statistically significant at the 0.05 level (using Scheffe's d procedure, with a

TABLE II

Peak Rate of Wall Thickening (dTw/dt) During Systole in Four Patients With Two Left Ventriculograms 5 to 10 Minutes Apart and No Nitroglycerin

	Peak dTw/dt			
	First Angiogram		Second Angiogram	
Case no.	Antero-septal Segment	Postero-lateral Segment	Antero-septal Segment	Postero-lateral Segment
24	4.8	...	5.4	...
25	4.2	9.6	4.8	10.8
26	3.6	...	3.0	...
27	...	7.8	...	7.8

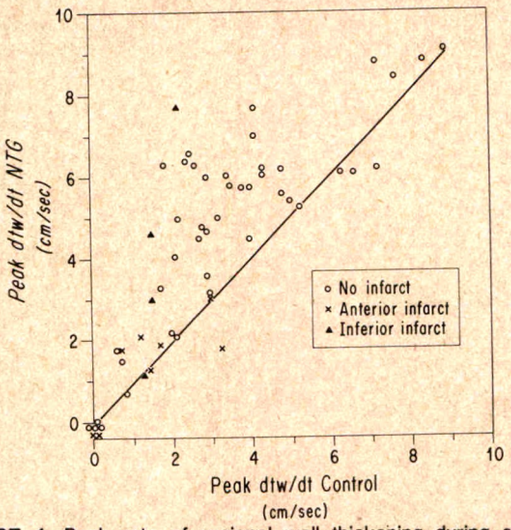

FIGURE 1. Peak rate of regional wall thickening during systole (dtw/dt) before **(abscissa)** and after **(ordinate)** administration of nitroglycerin (NTG). **Circles** represent segments considered to show no electrocardiographic evidence of myocardial infarction; **crosses** and **triangles** represent, respectively, segments with electrocardiographic evidence of anterior and inferior myocardial infarction.

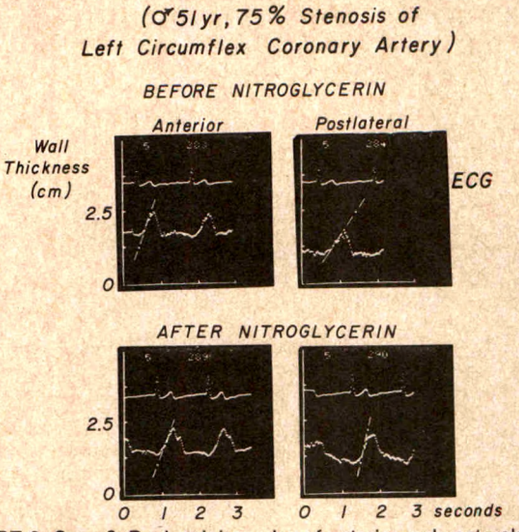

FIGURE 2. Case 3. Regional dynamics of anterior and posterolateral ventricular wall thickness before and after administration of nitroglycerin. The peak rate of thickening of the anterior wall **(left),** which was initially normal, did not change after nitroglycerin, whereas the peak rate of thickening of the posterolateral wall **(right),** initially hypokinetic (less than 5 cm/sec), was normal (more than 5 cm/sec) after nitroglycerin.

two-sided test). However, after administration of nitroglycerin, the mean and standard deviation of change in dTw/dt for 15 posterior segments without infarction were 1.41 and 1.34, respectively, and for 6 posterior segments with infarction, 1.68 and 2.24 (difference not statistically significant at the 0.05 level).

Group II—patients with normal coronary arteries and nitroglycerin studies: Two patients had angiographically normal coronary arteries. Changes in hemodynamic data, ejection fraction and end-diastolic volume are listed in Table I. In the four normal regions studied, the range of change in peak dTw/dt was −0.6 to +0.9 cm/sec. The maximal difference in peak dTw/dt between anterior and posterior regions studied in the same ventricle was 0.6 cm/sec before and 0.3 cm/sec after administration of nitroglycerin.

Group III—patients with two ventriculograms but no nitroglycerin before second left ventriculogram: Data from four patients without an intervention between left ventriculograms performed 5 to 10 minutes apart are included in Table II. The difference in peak dTw/dt in the same segment without an intervention ranged from 0 to 1.2 cm/sec, with a mean of 0.6 cm/sec in the five segments available for such studies. The maximal difference between any two segments was 20 percent of the smallest value for peak dTw/dt. Three segments showed a small increase, one a decrease and one no change in peak dTw/dt.

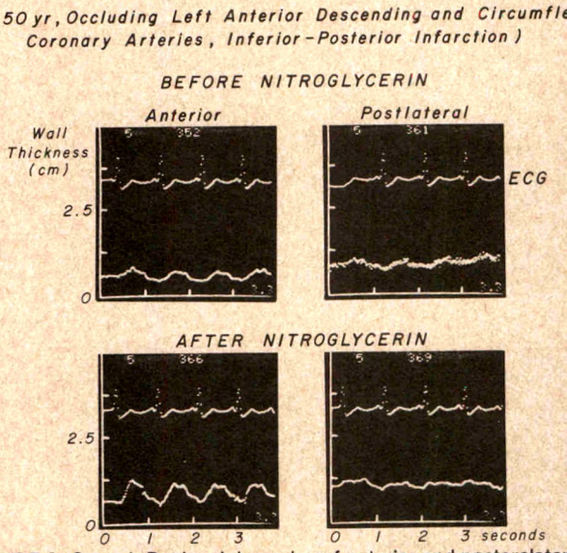

FIGURE 3. Case 4. Regional dynamics of anterior and posterolateral ventricular walls before and after administration of nitroglycerin. Both regions were originally hypokinetic. A selective increase in the peak systolic rate of thickening of the anterior wall occurred after nitroglycerin.

Discussion

The method used for the quantitative evaluation of regional wall dynamics in this study has been described in detail recently.[7] Regional wall dynamics were quantitated by measuring wall thickness, percent change of wall thickness during systole and the mean and peak rates of wall thickening. The peak rate of wall thickening (peak dTw/dt) reliably differentiated normal patients from those with uniform reduction of left ventricular contraction. Also, in selected patients with coronary artery disease and regional abnormalities of contraction, a good correlation was found between the anatomic location of a coronary arterial stenosis and the region with a quantitative

abnormality of peak dTw/dt. Thus, the peak rate of wall thickening during systole appeared to provide a quantitative index of regional left ventricular functional status.

Any study of sequential left ventriculograms requires consideration of the effect of the prior dose of contrast material on the data derived from the second left ventriculogram. The hemodynamic effects of contrast media, which have been extensively documented,[10,11] include increases in cardiac output, plasma circulating blood volume and ventricular end-diastolic pressure. Some of these alterations may persist for 20 minutes after the injection of contrast material. We used a time interval of 10 minutes between the two left ventriculograms to minimize the duration of the procedure. The validity of this approach is supported by the small variation in the peak dTw/dt and in the two ventriculograms obtained in the patients without administration of nitroglycerin. This corresponds to the findings of Brown et al.,[10] who noted that mean cardiac output returned to approximately 10 percent above control level 10 to 15 minutes after angiocardiography.

Reversibility of Abnormal Regional Wall Dynamics

Having demonstrated the feasibility of quantitating abnormalities in wall dynamics with the videometric system, we investigated the reversibility of regional abnormal rates of wall thickening at rest after administration of nitroglycerin to patients with coronary artery disease. The number of reports on attempts to improve regional abnormalities of contraction at rest has been increasing. Herman et al.[12] emphasized the importance of regional abnormalities of contraction in patients with coronary artery disease, and Herman and Gorlin[13] reported improvement in an area of paradoxic pulsation after administration of epinephrine. Belousov et al.[14] noted electrokymographic improvement in areas of abnormal pulsation after administration of nitroglycerin in 11 patients with coronary artery disease. More recently, Helfant et al.[15] demonstrated improvement in hypokinetic and akinetic regions of the left ventricular wall after nitroglycerin in 35 patients with coronary heart disease; on the basis of these data, they suggested that the presence of regional residual contractility can be predicted. Most previous studies of the effect of an intervention on regional patterns of contraction have been directed toward the development of an abnormality in a region that appeared to be normal at rest. Dwyer[16] studied the appearance and pressure-volume relations of the left ventricle during angina pectoris induced by atrial pacing. In 8 of 10 such patients, gross alterations in regional patterns of contraction were observed, with an associated narrowed coronary artery supplying the affected region. The most frequent abnormality was a reduction in degree of wall motion. Helfant et al.[17] studied the effect of propranolol, 5 mg intravenously, on left ventricular contraction and noted that asynergy was induced in five subjects, three of whom had coronary artery disease. Dove et al.[18] demonstrated in eight patients with coronary artery disease that regional hypokinesia and akinesia elicited by atrial pacing could be returned toward a state of normal kinetics when nitroglycerin was administered during the pacing.

Determinants of reversibility after nitroglycerin: This study has shown that hypokinetic areas of the left ventricle (specifically defined as areas with a peak systolic rate of wall thickening (dTw/dt) of less than 5 cm/sec but greater than 0) in patients with coronary artery disease show improvement or return to normal after administration of nitroglycerin. A critical determinant of this response appears to be the state of the muscle in the region under study. Thus, within the same ventricle, and with identical hemodynamic and volumetric changes, some abnormal areas may show improvement while others are not changed. Hypokinetic areas within the expected anatomic distribution of myocardial infarction, as determined by electrocardiography, had lower rates of wall thickening and did not increase to the same degree as did areas without infarction. The exceptions to this generalization occurred primarily in patients with an electrocardiographic classification of inferior myocardial infarction, when the operator of the videometric system was uncertain about the anatomic extent of the inferior infarction on the posterior lateral wall segment being sampled. An additional consideration is that areas with electrocardiographic evidence of myocardial infarction in which there is a dramatic improvement in hypokinetic areas may represent sites of ischemic but viable muscle surrounding the infarcted area.

Mechanism of Nitroglycerin Effect

Increased coronary blood flow: The mechanism of increased rate of wall thickening in regional areas of the left ventricle presumed to be ischemic secondary to significant coronary arterial narrowing is not clear from our study. An increase in coronary blood flow after administration of nitroglycerin has been shown by Abel and Reis[19] to increase myocardial contractility. These investigators used an isovolumetrically contracting dog ventricle so that coronary blood flow and pressure could be controlled independently. A change in myocardial contractility was assessed by comparison of force-velocity curves with calculated changes in velocity of shortening of the contractile element. With coronary arterial pressure held constant, myocardial contractility increased with the increase in coronary blood flow after administration of nitroglycerin. They considered the possibility of a direct action of nitroglycerin on cardiac muscle as an explanation of these findings but referred to unpublished observations of Zelis that nitroglycerin had no effect on the contractile state of the isolated papillary muscle.

Redistribution of myocardial blood flow: Also to be considered is the possibility of redistribution of myocardial blood flow to ischemic areas during administration of nitroglycerin. Winbury et al.[6] demonstrated evidence of redistribution of coronary blood flow after administration of nitroglycerin. Using a

polarographic technique to measure oxygen tensions in the subepicardium and subendocardium, they demonstrated that, after nitroglycerin, oxygen tension in the subendocardium increased markedly, with little or no change in subepicardial oxygen tension, both in normal animals and in animals with experimental subendocardial ischemia. They concluded that nitroglycerin resulted in a diversion of blood flow from the subepicardium to the subendocardium. In contrast, Forman et al.[20] demonstrated that dogs with acute partial coronary occlusion had a significant decrease in subendocardial blood flow after nitroglycerin, with diversion of blood to the subepicardial areas. This finding was supported by the measurement of contractile force in subendocardial and subepicardial areas and the demonstration of a reduction of contractile force in the deep subendocardial layers of the ventricle after nitroglycerin.

Interpretation of these findings in relation to our findings is difficult for three reasons: (1) The regional wall dynamics measured in our study cannot necessarily be equated with force of contraction; (2) subendocardial and subepicardial sections of the segment of the ventricle under study cannot be differentiated by the technique used; and (3) there are obvious differences between patients with chronic ischemic heart disease and dogs with acute experimental coronary arterial occlusion. It is also possible that the changes in regional left ventricular wall function noted in our study were related to alterations in afterload as a result of the nitroglycerin.

Peripheral effects—reduced myocardial oxygen requirements: Previous studies[21] have emphasized the peripheral actions of nitroglycerin as a major factor in the beneficial effect of the drug in patients with coronary artery disease. The decrease in overall wall tension as a result of a decrease in ventricular volume and wall tension throughout the cardiac cycle results in a reduction in myocardial oxygen requirements that may be of importance to the ischemic ventricle. Our study provides evidence of a regional myocardial response to nitroglycerin with differing responses within the same ventricle apparently depending upon the functional state of the underlying myocardium.

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Effects of Nitroglycerin on the Major Determinants of Myocardial Oxygen Consumption

An Angiographic and Hemodynamic Assessment

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A direct and quantitative study of the effects of sublingually administered nitroglycerin on the major determinants of myocardial oxygen consumption was carried out in 10 patients, 7 with coronary artery disease. Left ventricular wall tension, estimates of the contractile state and heart rate were studied directly using simultaneous pressure measurements and angiographically obtained volume determinations.

The peak systolic left ventricular wall tension decreased 15 percent after administration of nitroglycerin, suggesting a diminished myocardial oxygen requirement. Increased myocardial oxygen requirements were suggested by the occurrence of both positive chronotropic and inotropic effects. Heart rate increased 15 percent. The mean circumferential fiber shortening velocity increased 26 percent and the ejection fraction 30 percent; these findings, in association with a 23 percent reduction in left ventricular end-diastolic volume, were considered consistent with an increase in the contractile state. The mechanism of action of nitroglycerin seems to relate best to the decrease in systolic wall tension. The end-diastolic tension decreased 57 percent, suggesting the possibility that diastolic coronary blood flow may be augmented by diminished extravascular resistance to flow.

Although nitroglycerin has been used for more than 100 years in the clinical management of angina pectoris,[1] its mechanism of action is not completely delineated. One hypothesis is that nitroglycerin favorably alters the relation between myocardial oxygen need and demand by favorably altering the determinants of myocardial oxygen consumption.[2] The second hypothesis is that nitroglycerin improves oxygen delivery to ischemic tissue by increasing total myocardial blood flow or by producing a redistribution of flow.[3]

The relation between oxygen supply and demand in patients with symptomatic coronary artery disease is determined by a restricted oxygen supply caused by a critical degree of coronary arterial stenosis. For this reason, therapeutic attempts have focused on reducing oxygen requirements. Myocardial oxygen requirements are determined to the greatest extent by heart rate, systolic pressure, left ventricular volume, left ventricular wall thickness and the contractile state of the left ventricle.

In all previous investigations of the mode of action of nitroglycerin, one or several determinants of myocardial oxygen consumption have been analyzed by indirect techniques, such as chest X-ray film,[4] indicator-dilution technique,[5] epicardial clips[6] or echocardiography.[7] In this study we made direct and simultaneous observations of each determinant of oxygen consumption to assess its relative importance.

Methods

The subjects were eight men and two women aged 39 to 62 years. Seven patients had coronary artery disease and three of these had a ventricular aneurysm. Of the three patients without coronary artery disease, two had a pri-

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mary myocardial disorder, manifested only by abnormal left ventricular end-diastolic pressure at rest or after exercise, and one had normal cardiac findings. Because the data in these 3 patients were directionally and quantitatively similar to those of the patients with coronary artery disease, the 10 patients were analyzed as one group.

Hemodynamic measurements: All patients were studied in a postabsorbtive state and were premedicated with 100 mg of orally administered pentobarbital sodium. Informed consent was obtained from each patient. A Teflon® needle was inserted percutaneously into the left brachial artery, and right and retrograde left heart catheterization was performed utilizing standard techniques. Observations of heart rate, brachial arterial pressure, left ventricular pressure and cardiac output were made during a 20 minute control period with the patient in a supine position. The zero reference pressure was set at mid-chest level. Pressures were measured with Statham strain gauge transducers (P23 Db series). Cardiac output determinations were made just before ventriculography by the dye-dilution technique with injection of indocyanine green dye into the pulmonary artery and sampling from the brachial artery.

The left ventricular end-diastolic pressure was measured at the trough formed by the downstroke of the *a* wave and the upstroke of the left ventricular pressure curve. In all instances this point was sharp and precise.

Angiographic measurements: An end-inspiratory left ventriculogram was obtained with the patient rotated into a 25° to 30° right anterior oblique position by a calibrated mechanical cradle. After injection of 50 to 60 cc of meglumine diatrizoate with sodium diatrizoate (Renografin®-76) into the pulmonary artery, a cine film (64 frames/sec) of the levophase was recorded. During ventriculography, left ventricular pressure, brachial arterial pressure and the electrocardiogram were recorded simultaneously at 200 mm/sec on a photographic recorder that also directly recorded the pressure on cine film using the Cinetrace system (Electronics for Medicine). To minimize the effects of contrast material on ventricular function the earliest systoles providing adequate visualization of the left ventricular cavity were analyzed. In light of our own observations and those of others,[8] approximately 25 minutes was allowed between ventriculograms to permit normalization of the hemodynamic state.

Hemodynamic and angiographic studies were repeated 3 to 6 minutes after sublingual administration of 0.6 mg of nitroglycerin. Subsequently, selective cineangiography of the right and left coronary arteries was performed in multiple projections by the Sones technique.

Calibration of all measurements in each ventriculogram to actual dimensions was done by positioning a grid with 1 cm markings at the level of the cardiac apex so that a single factor (f) could be calculated to correct for magnification.

The silhouette of the left ventricular end-diastolic cavity was drawn and outlined. The area (A) within the left ventricular outline was obtained by planimetry. The long axis (L) from the apex to the mid-plane of the mitral valve was measured directly. The average width (W) of the short axis was then calculated from the equation for the area of an eclipse where $W = 4A/L$.

Left ventricular end-diastolic volume was calculated from the single plane cine film using the ellipsoid model and method described by Greene et al.[9] The formula used in each instance is: $V = \pi/6 \cdot 1/f^3 \cdot LW^2$, where V = volume, f = magnification factor, L = long axis and W = short axis.

Ejection fraction: Stroke volume was calculated by dividing the dye-dilution cardiac output determination by heart rate. The dye-dilution value for stroke volume was used in conjunction with the angiographically determined end-diastolic volume to calculate ejection fraction. The ejection fraction, so determined, is usually less (normal = 45 ± 6 [mean ± standard deviation] percent) than the ejection fraction calculated solely by the angiographic technique. We elected to calculate ejection fraction with this method for several reasons. We and others[10] have observed occasional difficulties in accurately outlining the complete ventricular silhouette, especially the area of the papillary muscles, although internal radii of the minor left ventricular circumference can be reproducibly measured (see later). Gentzler et al.[11] have shown that, although left ventricular end-diastolic volume measurements are identical in posteroanterior and lateral angiograms, values for end-systolic volume vary widely in the two projections in patients with regional wall abnormalities. This technique eliminates potential error introduced by regional wall abnormalities not visualized when angiographic studies are limited to a single plane.

Ventricular axes and wall thickness: The internal radius of the minor left ventricular circumference was measured at 31.2 msec intervals and at a point perpendicular to and at the mid-point of the long axis. Left ventricular wall thickness and the long axis were measured at end-diastole and end-systole and then the intermediate points were calculated, assuming a linear change in wall thickness and length.[12] Because there was a time lag of 30 msec in the catheter and transducer system, the left ventricular pressure data recorded on the cine film were appropriately corrected for the calculation of wall tension.

Wall tension: The geometric reference figure used to calculate wall tension was a thick-walled ellipse. Left ventricular wall tension was computed throughout systole with the aid of a digital computer as

$$\text{Wall tension} = P\ ri\left(\frac{1 - 2ri^2}{L^2}\right)\Big/ h$$

where P = left ventricular intracavitary pressure in millimeters of mercury, ri = instantaneous internal radius in centimeters, L = long axis in centimeters and h = wall thickness in centimeters.

The distribution of force across the myocardial wall is unknown but is generally assumed to be uniform throughout the myocardial wall. Such an assumption is clearly invalid in many of the patients in our study, who have residual infarcts, areas of wall thinning or dyskinetic motion. Unless such regional changes are recognized, wall tension will be seriously underestimated. Wall tension in this study refers only to the mean tension generated by a cross section of myocardium through the equator of the ellipse.

End-diastolic tension (EDT), peak systolic tension (PST) and peak developed tension (PDT) where PDT = PST − EDT were calculated.

Velocity of shortening (V_{CF}): A mean velocity of shortening of the internal circumference was computed in each patient by dividing the extent of shortening of the mid-wall circumference by the systolic ejection time. This calculation was corrected for end-diastolic circumference so that the mean velocity of circumferential fiber shortening was expressed as circumferences per second. Estimates of systolic performance of the left ventricle based on determinations of ejection fraction and V_{CF} have been shown by Gentzler et al.[11] to vary with the angiographic view in patients with regional wall abnormalities. This variability is

TABLE I

Summary of Data Before and After Sublingual Administration of Nitroglycerin

Case no.	BSA	Age (yr) & Sex	State	Diagnosis	HR	LVS/ED	CI	SI	SEP	EDVI	EDT	PST	PDT	EF	$\overline{V}_{CF}$
1	1.94	45M	C	CAD	70	110/19	3.4	49	0.32	85	49	192	143	58	0.95
			NTG		79	105/15	4.5	57	0.32	67	28	124	96	85	1.29
2	1.64	49M	C	CAD	75	80/18	3.4	45	0.29	146	64	264	220	31	0.47
			NTG		90	75/10	3.3	37	0.26	129	35	228	193	28	0.84
3	1.83	52M	C	CAD	104	102/8	3.4	33	0.26	113	17	207	190	29	1.94
			NTG		110	100/6	3.9	36	0.24	80	13	182	169	45	2.01
4	1.73	48M	C	CAD	90	150/16	4.0	45	0.28	87	47	347	300	52	1.07
			NTG		120	135/7	5.5	46	0.26	83	18	223	205	55	1.19
5	1.81	62M	C	CAD	75	100/15	3.0	40	0.28	215	59	328	269	10	0.38
			NTG		76	90/9	2.6	29	0.28	120	26	243	217	24	0.60
6	1.80	58M	C	CAD	71	122/21	2.2	32	0.29	220	70	355	285	14	0.22
			NTG		72	100/10	2.0	29	0.28	189	35	289	254	15	0.34
7	1.50	60F	C	CAD	70	150/15	2.9	41	0.34	86	48	296	248	48	0.92
			NTG		75	145/9	3.1	42	0.32	75	21	232	211	56	1.12
8	1.94	39M	C	PMD	84	135/13	3.3	39	0.30	102	27	180	153	39	1.74
			NTG		116	NA/4	4.1	35	0.20	72	7	NA	NA	49	2.45
9	1.59	50F	C	PMD	72	185/25	3.0	42	0.32	91	97	421	324	46	1.21
			NTG		80	140/7	3.5	44	0.32	69	21	291	270	64	1.50
10	1.57	57M	C	Normal	83	125/6	2.8	34	0.28	91	16	216	200	37	2.06
			NTG		92	110/4	2.5	28	0.26	60	8	164	156	47	2.55
Mean ±SEM			C		79 ±4	126/17 ±10/2	3.2 ±0.2	41 ±2	0.30 ±0.01	124 ±17	49 ±8	281 ±26	233 ±20	36 ±5	1.10 ±0.21
			NTG		91 ±6	111/9 ±9/1	3.6 ±0.3	39 ±3	0.28 ±0.01	94 ±13	21 ±3	220 ±18	197 ±17	47 ±6	1.39 ±0.24
P value					<0.01	<0.001	NS	NS	<0.05	<0.01	<0.01	<0.001	<0.001	<0.01	<0.001

BSA = body surface area (m^2); C = control; CAD = coronary artery disease; CI = cardiac index (liters/min per m^2); circ/sec = circumferences per second; EDT = end-diastolic tension (g/cm^2); EDVI = end-diastolic volume index (cc/m^2); EF = ejection fraction (%); HR = heart rate (beats/min); LVS/ED = left ventricular systolic/end-diastolic pressure (mm Hg); NTG = after nitroglycerin; NA = not available; NS = not significant; *P* = probability; PDT = peak developed tension (g/cm^2); PMD = primary myocardial disorder; PST = peak systolic tension (g/cm^2); SEM = standard error of the mean; SEP = systolic ejection period (sec); SI = stroke index (cc/m^2); $\overline{V}_{CF}$ = mean circumferential fiber shortening velocity (circumferences/sec).

caused by inconsistency in measurement of end-systolic volume, which use of the indicator-dilution technique obviates. In addition, in each instance in our study each patient served as his own control, and identical oblique views were obtained before and after administration of nitroglycerin.

Results

Each of the major determinants of myocardial oxygen consumption ($M\dot{V}O_2$) was studied (Table I, Fig. 1):

Hemodynamic Measurements

Heart rate, which is considered a major determinant of myocardial oxygen consumption, increased 15 percent after administration of nitroglycerin, from 79 to 91 beats/min (P <0.01). Two patients with three vessel coronary artery disease and a ventricular aneurysm showed only minimal changes (1 to 2 beats/min).

Left ventricular systolic pressure decreased from a mean value of 126 to 111 mm Hg (P <0.01). This variable contributes considerably to developed wall tension, a major determinant of $M\dot{V}O_2$, and is examined in detail later.

Cardiac index and stroke index relate poorly to oxygen requirements, and neither showed a significant change after administration of nitroglycerin.

Left ventricular end-diastolic pressure was elevated (17 mm Hg) during the resting state in these patients. After the administration of nitroglycerin it decreased significantly to 9 mm Hg (P <0.001), most likely reflecting the decrease in left ventricular volume.

Left Ventricular Volume

The left ventricular cavity size decreased from 124 to 94 cc/m^2 (P <0.01) after administration of nitroglycerin. In general there was a reduction in both the long and short axes; in two patients there was a slight increase in the long axis associated with a marked decrease in mid-plane diameter.

Left ventricular wall tension: Instantaneous left ventricular wall tension is a major determinant of $M\dot{V}O_2$ and is calculated from combined measurements of left ventricular pressure, cavity size and

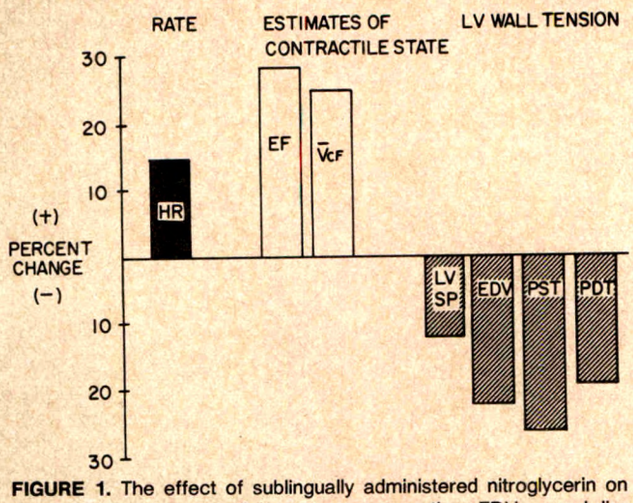

FIGURE 1. The effect of sublingually administered nitroglycerin on determinants of myocardial oxygen consumption. EDV = end-diastolic volume; EF = ejection fraction; HR = heart rate; LV = left ventricular; LVSP = left ventricular systolic pressure; PDT = peak developed tension; PST = peak systolic tension; $\bar{V}_{CF}$ = mean circumferential fiber shortening velocity.

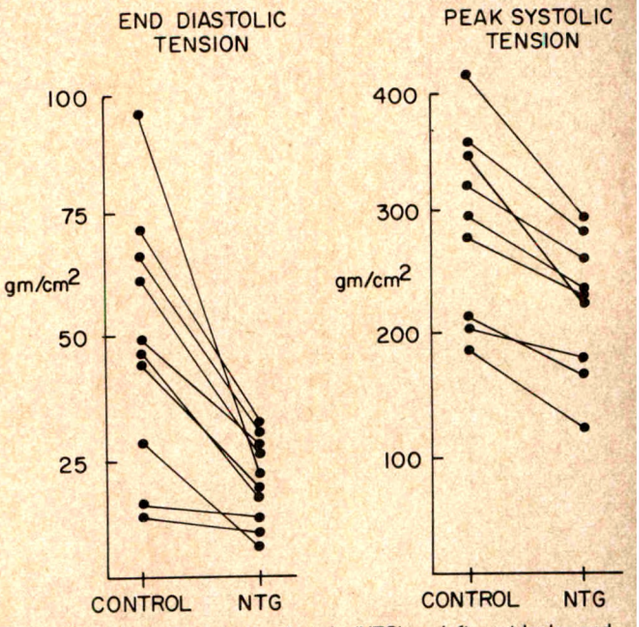

FIGURE 2. The effect of nitroglycerin (NTG) on left ventricular end-diastolic and peak systolic tension values for each patient. The end-diastolic tension is reduced from 49 ±8 (standard error of the mean) to 21 ±3 g/cm^2 (P <0.01) and the peak systolic tension from 281 ±26 to 220 ±18 g/cm^2 (P <0.001). Note that both tension levels fall in all patients.

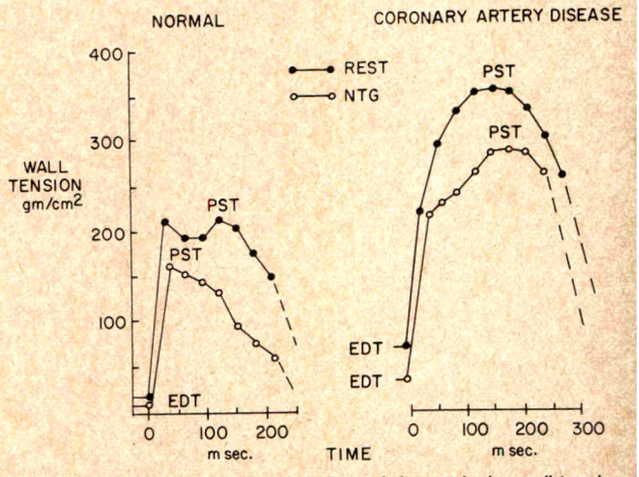

FIGURE 3. The effect of nitroglycerin on left ventricular wall tension in a normal subject (Case 10) and a patient with coronary artery disease (Case 3). Wall tension is plotted at 31.2 msec intervals (2 cine frames) beginning with end-diastole, a point determined from the left ventricular pressure curve on the cineangiogram. Tension is reduced through systole after administration of nitroglycerin and there does not appear to be any significant change in time to peak systolic tension (PST). EDT = end-diastolic tension.

wall thickness. End-diastolic tension, peak systolic tension and peak developed tension were also evaluated.

After administration of nitroglycerin, end-diastolic wall tension decreased from 49 to 21 g/cm^2 (P <0.01), peak systolic tension from 281 to 220 g/cm^2 (P <0.001) and peak developed tension from 233 to 197 g/cm^2 (P <0.001). All 10 patients had decreases in all three tension measurements. Figure 2 plots for each patient the decrease in end-diastolic and peak systolic tension values after administration of nitroglycerin. Figure 3 shows the time course of wall tension development before and after nitroglycerin in both a normal patient (Case 10) and a patient with coronary artery disease (Case 3). In patients with severe coronary disease, and particularly in those with a ventricular aneurysm, there was a considerable delay in the time to peak tension, often as great as 150 to 160 msec. Administration of nitroglycerin did not change the time to peak tension in any patient. A more rapid reduction in wall tension was frequently observed after nitroglycerin was given.

Contractile State of the Left Ventricle

The contractile state of the left ventricle was estimated by determination of ejection fraction and mean circumferential fiber shortening rate ($\bar{V}_{CF}$). Increases in both variables strongly suggested an increase in the contractile state after administration of nitroglycerin particularly since the left ventricular end-diastolic volume diminished concurrently.

By our method of calculating ejection fraction (dye-dilution stroke volume and angiographic end-diastolic volume) four patients, all with coronary artery disease, had a reduced ejection fraction. Two of these patients had a substantial increase in ejection fraction and two manifested little change after administration of nitroglycerin. The remaining patients with a normal resting ejection fraction showed increases. For the entire group, the mean ejection fraction increased from 36 to 47 percent (P <0.01) after nitroglycerin, representing an increase of approximately one third.

Mean V_{CF} increased in all patients, changing from a mean control value of 1.10 to 1.39 circumferences/sec (P <0.001). The mean resting value was below the

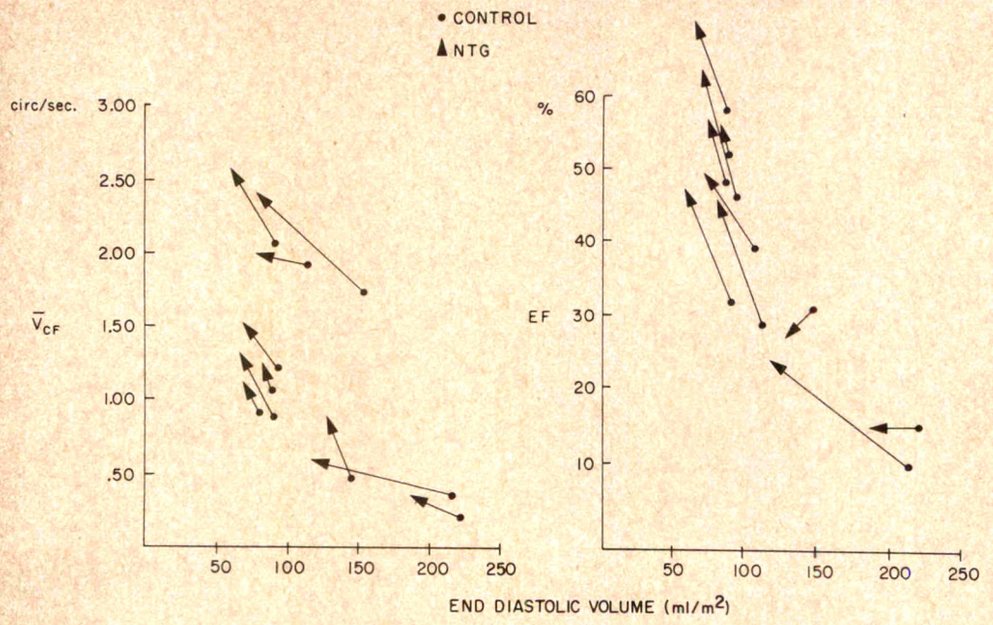

FIGURE 4. The effect of nitroglycerin on measurements that estimate the left ventricular contractile state. The mean circumferential fiber shortening velocity ($\bar{V}_{CF}$) increases in each patient after the administration of nitroglycerin whereas end-diastolic volume diminishes. Similarly, the ejection fraction (EF) increases with diminishing end-diastolic volume in all but one patient (Case 2).

normal mean value of 1.50 circumferences/sec reported by Karliner et al.[13] Only one of the patients with coronary artery disease had a normal resting value. The increase in mean V_{CF} and ejection fraction after administration of nitroglycerin was associated with a decrease in left ventricular volume in each patient (Fig. 4).

Discussion

The direct quantitation of myocardial oxygen consumption ($M\dot{V}O_2$) requires the measurement of myocardial blood flow and oxygen content of arterial and coronary venous blood. The arteriovenous oxygen difference can be determined with minimal error and is unchanged after administration of nitroglycerin in patients with coronary artery disease.[14] However, because results of determinations of myocardial blood flow after administration of nitroglycerin to patients with coronary disease have been variable,[15,16] the effect of nitroglycerin on $M\dot{V}O_2$ has remained uncertain. In addition, the distribution of blood flow to the left ventricle of patients with coronary disease is heterogeneous,[17] and changes in total $M\dot{V}O_2$ may not reflect local alterations in $M\dot{V}O_2$ since wide variations in flow or arteriovenous oxygen difference may occur in relation to localized coronary arterial narrowings.[18] In spite of these limitations, a majority of studies, utilizing a variety of techniques including inert gases,[15] nitrous oxide,[14] flowmeters[19] and thermodilution,[20] have shown a slight decrease in flow and $M\dot{V}O_2$ after administration of nitroglycerin. Unpublished data from our laboratory in which total and regional flow was measured by the xenon-133 washout technique[21] confirm these observations.

Previous investigations of the effect of nitroglycerin on the determinants of oxygen consumption have utilized indirect indexes or have not analyzed all factors that contribute significantly to oxygen consumption (for example, contractile state).[22] In this study, simultaneous measurements of left ventricular wall tension, estimates of the contractile state and determinations of heart rate were performed to provide a more comprehensive assessment of the effect of nitroglycerin in relieving angina.

Decreased wall tension and $M\dot{V}O_2$ after nitroglycerin: Left ventricular wall tension was determined directly by simultaneous pressure-volume measurements. We analyzed systolic, diastolic and peak developed wall tension before and after administration of nitroglycerin. Peak developed tension has been established in experimental studies[23] as the tension factor that bears the closest relation to myocardial oxygen consumption. After administration of nitroglycerin to our patients, we observed an 18 percent reduction in peak developed tension commensurate with significant reductions in end-diastolic volume and systolic pressure. Graham et al.,[23] using anesthetized animals, analyzed the relation of peak developed tension and $M\dot{V}O_2$ (with a constant contractile state). They demonstrated a change of approximately 25 to 30 percent in $M\dot{V}O_2$ for every 100 percent change in peak developed tension. Extrapolation of their data to our observations suggests that the reduction in wall tension observed after administration of nitroglycerin would result in only a 4 to 6 percent reduction in $M\dot{V}O_2$. However, nitroglycerin will reduce wall tension to a greater extent in the inner layers of the left ventricle and thus may produce a relatively greater decrease in endocardial oxygen requirements. During these studies we also observed increased wall motion in some local regions of the left ventricle (unpublished data), as others[24] have reported. The combination of diminished heart size and increased systolic wall motion produced by nitroglycerin should reduce systolic wall tension to an even greater extent, particularly in regions that may

be ischemic and hypokinetic at rest. The net effect would be to reduce oxygen demand in the most vulnerable regions of the myocardium. Of course, our analysis of changes in wall tension refers only to the mid-wall of the left ventricle. In patients with coronary artery disease, dyskinetic and hypokinetic regions outside the mid-portion of the left ventricle will show a relatively greater wall tension than that seen in normally contracting areas.

Inotropic effects of nitroglycerin—improved contractile state: The contractile state of the left ventricle has a significant effect on $M\dot{V}O_2$,[22] and this state is difficult to characterize in man. Recently, the use of isovolumetric indexes to determine contractility has been questioned on technical[25] and theoretical[26] grounds; therefore we elected to estimate the inotropic state of these patients with measurements of mean V_{CF} and ejection fraction, both of which rely on angiographic techniques and represent the ejection phase of ventricular contraction. Both ejection fraction and mean V_{CF} increased 25 to 30 percent after sublingual administration of nitroglycerin. Earlier investigations have suggested that nitroglycerin produces an increase in contractility in anesthetized[27] and unanesthetized[28] canine preparations, in isolated human atrial and ventricular myocardium[29] and in hemodynamic studies in man.[30] Sympathectomy[27] and beta adrenergic blockade[28,30] both appear to abolish this effect, thus suggesting that the positive inotropic response results from sympathetic reflex activity induced by hypotension or cardiac receptors that are sensitive to diminishing heart size.[31] The change we observed in the contractile state was probably not due to the small increase in heart rate. Higgins et al.[32] have shown in the conscious animal undergoing cardiac pacing that an increase in heart rate of this magnitude would not significantly increase myocardial contractility.

Redistribution of coronary blood flow after nitroglycerin: One of the most dramatic and consistent effects of nitroglycerin was a marked (57 percent) decrease in end-diastolic wall tension (Fig. 2). Changes in diastolic wall tension would probably not influence oxygen demand; however, since they may influence the redistribution of myocardial blood flow, this alteration merits further discussion. Because earlier results[14,15,19,20] have raised serious questions regarding the hypothesis that nitroglycerin acts by increasing total coronary blood flow, consideration has been given the possibility that nitroglycerin may effect a redistribution of flow to or within the ischemic region.

One hypothesis that suggests redistribution of flow between epicardium and endocardium has been supported by recent studies of endocardial and epicardial flow distribution with the use of rubidium-86,[33] microspheres[34] and oxygen tension measurements.[19] Becker et al.[34] have demonstrated that disproportionate levels of perfusion and ischemia occur in the subendocardial layer under circumstances of reduced coronary flow and that administration of nitroglycerin results in a shift of flow from a relatively well perfused epicardium to a less adequately perfused endocardium. Our observation of changes in end-diastolic tension may be pertinent in this context.

It appears unlikely, in the presence of a critical stenosis of the coronary artery, that total nutrient flow would be increased by nitroglycerin. In addition, a maximal reduction of coronary arteriolar resistance results from ischemia, and an additional decrease in coronary arteriolar resistance would probably not be produced by nitroglycerin. However, resistance to flow may also be significantly reduced by a decrease in extravascular compressive forces such as that suggested by the pronounced reduction in diastolic tension. Salisbury et al.[35] and, more recently, Becker and Pitt[3] have emphasized the role of compressive extravascular forces in the production and relief of ischemia.

Under normal circumstances with normal perfusion pressure, intramural pressure offers little impedance to diastolic coronary flow. On the other hand, patients with coronary disease show an early marked increase in left ventricular filling pressure during exercise[36] that would contribute significantly to an increase in diastolic wall tension. In addition, the appearance of ischemia can be associated with an enlarging left ventricle,[37] which would also act to increase diastolic wall tension and impedance to diastolic flow. Our data suggest that the effective reduction in heart size produced by nitroglycerin not only may diminish oxygen demand by reducing systolic wall tension, but also may improve endocardial perfusion by decreasing diastolic extravascular resistance.

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Specificity of Elevated Serum MB Creatine Phosphokinase Activity in the Diagnosis of Acute Myocardial Infarction

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Creatine phosphokinase (CPK) isoenzyme determinations are useful in the diagnosis of myocardial infarction. However, until suitably sensitive and precise quantitative procedures became available, the diagnostic specificity of serum CPK isoenzyme elevations could not be thoroughly examined. In this study an assay procedure capable of accurately determining activity of individual CPK isoenzymes even in serum samples with normal total CPK activity was employed to obtain two types of information. First, CPK isoenzyme profiles were examined in extracts of a spectrum of human tissues obtained at operation to determine whether the isoenzyme associated with myocardium is present in other human tissues in quantities sufficient to produce increased activity in serum. In addition, CPK isoenzymes were analyzed quantitatively in serial serum samples from 50 hospitalized control subjects, 100 patients with acute myocardial infarction, 100 patients undergoing noncardiac surgery and 50 patients undergoing cardiac catheterization to determine whether insult to tissues other than the heart is associated with increased "myocardial" CPK isoenzyme activity in serum. Results from analyses of tissue extracts indicated that myocardium is the only tissue surveyed containing sufficient MB CPK to account for substantial increases in serum MB activity. Results from analyses of serial serum samples indicated that MB CPK activity levels are consistently elevated after myocardial infarction, averaging 0.089 IU/ml. However, after cardiac catheterization or noncardiac surgery peak serum MB activity remains low, averaging only 0.004 IU/ml despite marked elevations in total serum CPK activity. Thus, elevated serum MB CPK activity is a highly specific as well as sensitive criterion of myocardial injury.

Soon after the pioneering observations by Karmen et al.,[1] increased activity of selected serum enzymes became the established hallmark of acute myocardial infarction. Elevation of serum creatine phosphokinase levels (CPK) appears to be the most sensitive conventional serum enzyme criterion of acute myocardial infarction,[2–4] but false positive results occur with a frequency of approximately 15 percent.[3] Recent technical advances in CPK isoenzyme analysis led to the observation that increased activity of serum MB CPK (an isoenzyme associated with myocardium) is a useful index of acute myocardial infarction.[5,6] We[7] have shown that increased serum CPK activity after intramuscular injections is not associated with elevated MB CPK levels in contrast to the case after acute myocardial infarction, but the overall specificity of elevated serum MB CPK activity as a diagnostic criterion of myocardial infarction remains to be thoroughly elucidated.

In this study we sought to determine whether human tissue outside the heart contained sufficient amounts of MB CPK to account for appreciable elevations of MB CPK activity in serum. We have recently

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developed a quantitative procedure for assay of activity of individual CPK isoenzymes, with a sensitivity of 0.002 IU/ml and reproducibility of ±2 percent.[8] This technique, which avoids some potentially serious quantitative difficulties associated with conventional methods, was employed in this study to assay CPK isoenzymes in extracts of human tissues obtained freshly during surgery from the myocardium, skeletal muscle, brain, stomach, colon, small intestines, lung, spleen, liver and kidney and washed red blood cells. Although some estimates of CPK isoenzyme activity have been made previously in tissues obtained at necropsy, a systematic evaluation of CPK isoenzyme profiles in freshly obtained human tissues employing a quantitative assay procedure has not been available.

A second goal of this study was to determine whether insult to tissues other than the heart produced serum MB CPK changes simulating those seen in patients with acute myocardial infarction. Accordingly, CPK isoenzymes were assayed in serial serum samples from 100 patients with definite myocardial infarction, 100 patients undergoing thoracic, abdominal, orthopedic or genitourinary surgical procedures, 50 patients undergoing cardiac catheterization and 50 hospitalized control subjects. Results of analyses of human tissue extracts obtained at operation and of serial serum samples in these patients indicate that myocardium is the only human tissue containing sufficient MB CPK to account for substantial elevations of MB CPK levels in serum. They confirm previous observations indicating that consistent elevations of serum MB CPK activity accompany acute myocardial infarction[5,6] and they demonstrate that surgical trauma to organs other than the heart does not produce elevated serum MB CPK activity even when total CPK activity is markedly increased.[9]

Materials and Methods

Tissue and Serum Sampling Procedures

Fresh samples of human skeletal muscle (deltoid, pectoralis major, vastus medialis and rectus abdominis), myocardium, stomach, small intestines, colon, brain, lung, liver, spleen and kidney were obtained from patients at the time of surgery required for therapy or diagnosis. Samples were minced, suspended in 25 ml/g of homogenizing medium and homogenized in 0.25 molar sucrose; 0.01 molar Tris, pH 7.4; 0.001 molar ethyleneglycoltetraacetic acid (EGTA), pH 7.4; and 0.001 molar mercaptoethanol.

Blood samples were collected in 0.005 molar neutralized EGTA, centrifuged at 2,000 *g* for 10 minutes and decanted. Mercaptoethanol (0.005 molar) was added to avoid loss of CPK activity.

Patients Studied

Patients with acute myocardial infarction: Blood samples were obtained serially from 100 patients admitted to the Barnes Hospital Cardiac Care Unit with definite transmural myocardial infarction manifested by a typical history of chest pain, serial electrocardiographic changes with development of Q waves and characteristic serial changes in serum transaminase and lactic dehydrogenase (LDH). Blood samples were collected every 2 hours through a peripheral venous indwelling cannula for a total of 48 hours. Samples were assayed immediately for CPK isoenzyme activity or fast-frozen, stored at −20° C and assayed within 4 weeks. Samples stored under these conditions do not exhibit loss of activity for at least 6 weeks.[8]

Hospitalized control subjects: Samples were obtained in the same fashion from 50 patients admitted because of suspected but unconfirmed acute myocardial infarction who served as control subjects.

Patients undergoing noncardiac surgery: One hundred patients undergoing surgical procedures (Table I) were studied. None exhibited clinical or electrocardiographic evidence of myocardial infarction during hospitalization. Blood samples were obtained immediately before operation, as soon as possible after operation, and every 6 hours thereafter for 24 hours.

Patients undergoing cardiac catheterization: Fifty patients were studied after combined right and left heart catheterization with selective coronary arteriography and ventriculography. The studies were performed in 40 patients because of suspected coronary artery disease and in 10 because of valve disease. Coronary arteriography was performed by the Sones technique (36 cases) or the Judkins technique (14 cases). Before catheterization patients were medicated with pentobarbital sodium (Nembutal®), 100 mg, and diazepam (Valium®), 5 mg, given intramuscularly. Transitory chest pain occurred in 10 patients during catheterization, but no patient studied exhibited clinical or electrocardiographic evidence of definite myocardial infarction. Blood samples for CPK determinations were obtained before and after catheterization and at 2 hour intervals subsequently for 24 hours.

Biochemical Determinations

Total CPK activity was determined spectrophotometrically[7] in serum samples and in 50 μl aliquots of tissue extracts diluted with Tris, 0.01 molar, pH 7.4, and bovine serum albumin, 2 mg/ml, so that CPK activity was within the range of linearity of the assay. Samples were assayed with and without creatine phosphate as substrate to exclude contributions to apparent activity from myokinase and other moieties. CPK isoenzymes were assayed quantitatively with the kinetic fluorometric procedure recently described.[8] Results with this procedure are linear with respect to time and enzyme activity and reproducible within ±2 percent. As little as 0.002 IU/ml of each isoenzyme can be detected under conditions that avoid several difficulties associated with quantification of isoenzyme activity by fluorescence scanning of electrophoretic media. As reported previously, serum samples from normal subjects assayed under these conditions contain less than 0.004 IU/ml of MB CPK.

Results

CPK Isoenzyme Activity in Tissue Extracts

Total CPK activity and CPK isoenzyme activity in extracts of human skeletal muscle, heart, brain, stomach, small intestines, colon, liver, spleen, lung, kidney and red blood cells are shown in Figure 1. As can be seen, CPK activity (expressed as IU/g wet weight of tissue) is greatest in skeletal muscle, exceeding activity in myocardium by more than 300 percent. Substantial amounts of CPK activity occur only in skeletal muscle, heart, brain and gastrointestinal tract. CPK activity in lung and kidney is less than 3 percent of that in myocardium.

TABLE I

Noncardiac Surgical Procedures in Patients Studied

Procedure	Patients (no.)
Thoracic	
Pneumonectomy	20
Exploratory thoracotomy	5
Hiatus hernia repair	5
Abdominal	
Gastrectomy	20
Splenectomy	5
Intestinal bypass	6
Colectomy	7
Genitourinary	
Prostatectomy	16
Hysterectomy	6
Orthopedic	
Total hip replacement	4
Meniscectomy	3
Tendon repair	3
Total	100

Of the tissues surveyed, only myocardium contains significant amounts of MB CPK. Under the assay conditions used, only the MM isoenzyme was detectable in extracts of skeletal muscle.

Serum CPK Isoenzymes

Control hospitalized subjects: As previously reported with a smaller group of patients,[8] CPK activity in serum samples from hospitalized patients with suspected but unconfirmed acute myocardial infarction averaged 0.038 ± 0.011 (standard deviation) and MB CPK activity averaged 0.002 ± 0.001 IU/ml (Table II). No hospitalized control subject exhibited MB CPK activity exceeding 0.005 IU/ml.

Patients with myocardial infarction: All 100 patients with definite myocardial infarction exhibited elevated serum levels of total CPK activity. Peak activity averaged 0.852 ± 0.120 IU/ml (Table II). The mean interval between the initial elevation of serum CPK activity and the time of occurrence of peak activity was 15.2 ± 3 hours (range 10 to 18 hours). The interval from the time of onset of chest pain to the time when CPK activity first exceeded the normal range was 4 ± 2 hours. Elevated MB CPK activity was observed in all patients with acute myocardial infarction. Peak MB CPK activity averaged 0.089 ± 0.032 IU/ml (range 0.025 to 0.215). MB CPK activity was generally detectable by fluorescence scanning within 4 hours after the onset of chest pain, when total CPK activity had increased by 50 to 100 percent above control values. Modestly increased MB CPK activity was detected slightly earlier with the quantitative technique, often within 3 hours after the onset of chest pain. Peak MB and peak total CPK activity occurred at about the same time.

Patients undergoing noncardiac surgery: All patients in this group exhibited elevated serum levels of total CPK activity (Table II). However, MB CPK elevations were not detected in any of the serial samples from these patients. Only MM CPK was detectable by electrophoresis and, with the quantitative assay technique, only minimal increases in serum MB CPK activity could be demonstrated (peak 0.005 IU/ml or less). Peak total CPK activity in samples from these patients generally occurred approximately 12 hours after operation, averaging, 0.850 ± 0.260 IU/ml. Thus, despite markedly elevated serum levels of total CPK activity, serum MB CPK activity did not increase after noncardiac surgery.

Patients undergoing cardiac catheterization: Forty-two of the 50 patients undergoing diagnostic cardiac catheterization exhibited elevated serum CPK activity (Table II). Peak CPK activity in this group averaged 0.260 ± 0.033 IU/ml and occurred 12 to 24 hours after cardiac catheterization. No patient in this group exhibited elevated MB CPK activity when samples were analyzed by electrophoresis. The maximal level of MB CPK activity detected was 0.004 IU/ml or less.

TABLE II

Serum CPK and MB CPK Activity in Patients

Category	Patients (no.)	Mean Peak Total CPK Activity (IU/ml)	Mean Peak MB CPK Activity (IU/ml)
Hospitalized controls	50	0.038 ± 0.011	0.002 ± 0.001
Acute myocardial infarction	100	0.852 ± 0.120	0.089 ± 0.032
Post-cardiac catheterization	50	0.260 ± 0.033	0.004 ± 0.001
Post-surgery	100	0.850 ± 0.260	0.003 ± 0.001
Thoracic	30	1.260 ± 0.320	0.004 ± 0.001
Abdominal	38	0.760 ± 0.106	0.003 ± 0.001
Genitourinary	22	0.842 ± 0.220	0.002 ± 0.001
Orthopedic	10	0.540 ± 0.180	0.003 ± 0.001

Results are expressed as means ± standard deviation.

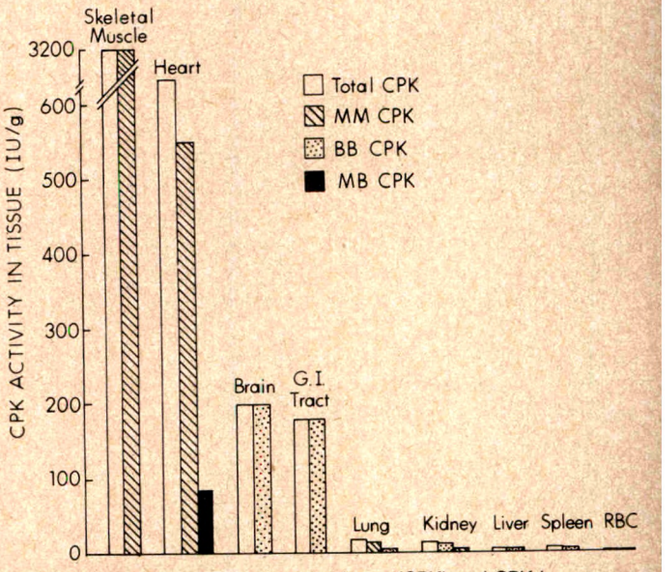

FIGURE 1. Total creatine phosphokinase (CPK) and CPK isoenzyme activity in extracts from human tissues obtained at operation. Results in each case represent averages based on analyses of tissue from at least four patients. Isoenzymes were analyzed in 10 μl aliquots of tissue extracts containing 0.5 IU/ml, under conditions in which 0.002 IU/ml was readily detectable. G.I. = gastrointestinal; RBC = red blood cells.

Discussion

It is well recognized that serum levels of total creatine phosphokinase (CPK) activity may increase after cardiac catheterization,[10] noncardiac surgery,[11] intramuscular injections,[12] pulmonary emboli,[13] inflammatory disease of muscle, muscular dystrophy, diabetic ketoacidosis, psychosis, seizure disorders and several other conditions.[4] Nevertheless, elevated serum CPK activity appears to be the most sensitive conventional enzyme criterion of acute myocardial infarction.[3] Three CPK isoenzymes, MM, MB and BB, have been detected consistently in tissue extracts.[14,15] With techniques utilizing electrophoresis coupled with fluorescence scanning, elevation of serum MB CPK activity has been shown to be a useful index of acute myocardial infarction.[5,16] In this study, we sought to evaluate the specificity of this index (1) by applying quantitative techniques only recently available to examine CPK isoenzyme patterns in extracts of fresh human tissues, and (2) by analyzing serum CPK isoenzyme patterns in serial samples from patients with acute myocardial infarction and patients undergoing noncardiac surgery or cardiac catheterization. CPK isoenzyme activity was assessed under conditions designed to avoid quantitative limitations inherent in assay techniques based on scanning electrophoretic media.[17] Our results indicate that only myocardial tissue contains appreciable amounts of MB CPK activity. Although serum MB CPK activity increases consistently after acute myocardial infarction, it does not increase after surgery or cardiac catheterization even when there are marked serum elevations of total CPK activity.

MM vs. MB CPK activity in skeletal muscle: Quantitative assessment of CPK isoenzyme activity in tissue extracts and in serum has been difficult. Results of several studies utilizing electrophoresis on agar,[14,18] agarose,[5,6] cellulose acetate[7,8] or polyacrylamide gel[19] indicate that skeletal muscle contains only the MM CPK isoenzyme. Analysis of CPK isoenzymes in skeletal muscle extracts by column chromatography supports this conclusion.[19] Small amounts of MB CPK activity have been observed in extracts of skeletal muscle in some previous studies,[15,20] However, freezing and thawing of samples may lead to conformational changes in the MM CPK molecule, altering its electrophoretic mobility and perhaps accounting for apparent MB activity.[15]

The MB and BB CPK isoenzymes may be more labile than MM CPK.[21] Hence, failure to observe isoenzymes of CPK other than MM in extracts of human skeletal muscle obtained at necropsy conceivably could result from autolysis with loss of MB and BB activity. Accordingly, all tissues analyzed in this study were obtained fresh at the time of operation. Under the conditions employed, no MB was detected in extracts of skeletal muscle.

The lack of availability of quantitative procedures for assay of individual CPK isoenzymes until recently made it difficult to avoid overloading electrophoretic media with one isoenzyme when detection of trace amounts of another was the goal. Overloading may produce apparent activity in the MB region despite the absence of MB CPK in the sample. In fact, trace amounts of MB CPK in extracts of skeletal muscle have been reported only when samples containing large amounts of CPK activity were analyzed.[15] In our study extracts of skeletal muscle obtained at operation contained no MB CPK. Even when media were overloaded with samples containing 12 IU/ml of total CPK, no apparent MB was detected. Thus, it is unlikely that substantial elevations of serum MB CPK activity could result from injury to skeletal muscle.

MB CPK activity after skeletal muscle injury: It is possible that specific skeletal muscles contain MB CPK. If this were the case, one would anticipate accumulation of MB CPK in serum after intramuscular injections or surgical trauma to the muscles. To evaluate this possibility, we analyzed serum CPK isoenzymes in patients undergoing surgery involving cervical, thoracic, abdominal, thigh and leg musculature. Despite markedly elevated total CPK activity in serum samples from many of these patients, elevation of MB CPK activity was never observed. These results, coupled with our previous observations in patients given intramuscular injections,[7] indicate that serum MB CPK activity is not elevated after injury to skeletal muscle sufficient to increase serum levels of total CPK activity markedly.

Serum levels of total CPK activity were consistently elevated but unaccompanied by increased MB CPK in serial samples from 50 patients undergoing cardiac catheterization. Increased activity of serum enzymes after cardiac catheterization[10,22] appears to reflect injury to skeletal muscle and subcutaneous tissues rather than to the heart. The absence of elevated MB CPK activity supports this conclusion. The detection of increased serum MB CPK activity should permit recognition of concurrent myocardial infarction in patients undergoing cardiac catheterization and should facilitate differentiation of serum CPK elevations associated with the procedure itself from those indicative of myocardial ischemic injury.

CPK isoenzymes after other tissue injury: Two organs exhibiting appreciable CPK activity besides the heart and skeletal muscle are the intestines and brain.[23] Analysis of CPK isoenzymes in these tissues indicated no detectable MB CPK (Fig. 1). MB CPK activity in serial serum samples from patients undergoing surgery of the gastrointestinal tract did not increase even when total CPK activity increased markedly. Serum CPK elevations associated with injury to the brain appear to reflect elevation of MM CPK activity, perhaps because of rapid disappearance of the BB isoenzyme from blood,[24] or because of release of MM CPK from skeletal muscle in response to insults to the central nervous system. Elevation of serum MB CPK activity has not been observed under these conditions.

Lung, kidney, liver and spleen extracts do not contain a great deal of CPK activity. The isoenzyme pat-

tern in these tissues includes no detectable MB CPK. Thus, it is not surprising that surgery involving these tissues is not associated with elevated serum MB CPK activity. Other investigators have reported increased serum MB activity in samples from most patients undergoing coronary revascularization—presumably indicative of myocardial injury associated with the procedure in patients with compromised coronary circulation.[25]

Results of this study indicate that the only human tissue containing substantial MB CPK activity is myocardium. The distinctive CPK isoenzyme pattern in myocardium contrasts with that of other enzymes such as LDH. For example, LDH_1, an isoenzyme associated with myocardial injury, is predominant in red blood cells, kidney and stomach as well as in myocardium.[4] Thus, elevated serum LDH_1 activity is a nonspecific criterion of myocardial injury.

Clinical implications: Elevated serum MB CPK activity is recognized as a useful index of acute myocardial infarction. Results of this study, coupled with previous observations, indicate that increased serum MB CPK activity is a remarkably specific reflection of myocardial injury as well. The only human tissue containing substantial amounts of MB CPK is myocardium. Surgical insults to organs other than the heart, even those containing large amounts of CPK, are not associated with increased serum MB CPK activity despite marked elevations of total CPK. Thus, elevated serum MB CPK activity appears to be a highly specific criterion of myocardial injury.

Acknowledgment

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The Functional Defect in Amyloid Heart Disease

The "Stiff Heart" Syndrome

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Left ventricular performance was studied in three patients with heart failure due to amyloid deposits. The diagnosis of amyloidosis was proved by cardiac biopsy in two patients and by rectal biopsy in the third. One patient had myelomatosis, but the other two had no other identifiable disease. The investigative technique allowed simultaneous measurements of pressure and volume in the left ventricle. The functional defect with slow cardiac filling at high pressure and greatly reduced left ventricular contraction differed from that of constrictive pericarditis and other heart muscle disease. These features of a "stiff heart" are probably unique to amyloidosis and should make possible positive recognition of the condition on the basis of echocardiographic, angiographic and hemodynamic findings.

Amyloid heart disease gives rise to a wide spectrum of disorders ranging from cardiac amyloidosis, in which the heart is severely affected but other systems relatively spared, to so-called senile cardiac amyloidosis in which clinical features are usually absent but amyloid deposits are found at postmortem study. In other cases, the heart is involved in a multisystemic disorder.

Pathologically, the heart is involved in the majority of patients with systemic amyloidosis. Brandt et al.[1] found amyloid in the heart of 90 percent of "primary" and myeloma-associated cases of amyloidosis and in 54 percent of cases of amyloidosis secondary to conditions such as rheumatoid arthritis, tuberculosis, osteomyelitis, bronchiectasis and lymphoma. However, it is unusual for the cardiac disorder to be the presenting feature in such cases although, at a later stage in the illness, clinical, radiologic or electrocardiographic evidence of cardiac involvement commonly develops.

The rarity of symptomatic cardiac amyloidosis is evident from the small number of cases studied at this hospital: Only 7 patients with clinically important cardiac amyloidosis were seen during a 15 year period in which more than 230 patients with hypertrophic cardiomyopathy and 150 patients with dilated cardiomyopathy were studied. Nevertheless, cardiac amyloidosis was the single most common cause of specific heart muscle disease. Only four patients with cardiac sarcoidosis, one patient with cardiac hemochromatosis, six patients with a serious cardiac disturbance associated with assorted neuromuscular disorders and six patients with various types of collagenosis were seen during this period.

The three patients studied presented within a 4 month period. They are described here because we could find no published studies of the functional abnormality caused by amyloid in the heart although clinical descriptions abound. Left ventricular pressure-volume relations in the three patients were studied by a new technique.

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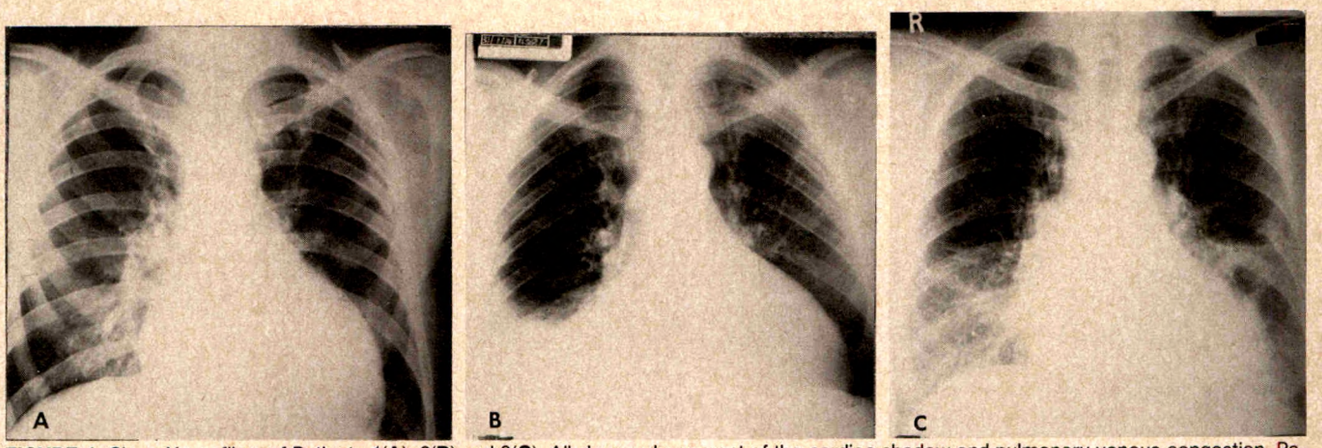


FIGURE 1. Chest X-ray films of Patients 1(**A**), 2(**B**) and 3(**C**). All show enlargement of the cardiac shadow and pulmonary venous congestion. Patients 1 and 2 had large pericardial effusions.

Case Reports

Case 1

A 44 year old man from Yugoslavia was admitted in November 1973. For 3 years he had had progressive exertional dyspnea and ankle edema with severe fatigue and weight loss. In Yugoslavia a fluctuating heart size had been noted on chest roentgenograms, and he had been studied there. Results of a rectal biopsy were reported to be normal.

Examination on admission revealed a chronically ill man with extremely low cardiac output. The arterial pulse was of strikingly small volume, and the blood pressure only 80/65 mm Hg. The heart rhythm was regular, and there was no pulsus paradoxus or alternans. The jugular venous pressure was 10 cm above the sternal angle with a dominant *y* descent. The cardiac impulse was impalpable. The heart sounds were faint with a widely split second heart sound but no third heart sound or murmurs. The lungs were clear. The liver was enlarged 4 cm below the right costal margin and nonpulsatile; there was no ascites or peripheral edema.

A chest X-ray film (Fig. 1A) showed an enlarged cardiac silhouette and slight pulmonary venous congestion. The electrocardiogram showed low voltage QRS complexes and a pattern of trifascicular block. The echocardiogram revealed a pericardial effusion and normal-sized left ventricle. A right atrial angiogram disclosed a large pericardial effusion. The diastolic pressure in the left ventricle was greatly increased but, although contraction was poor, the cavity was not dilated (Fig. 2, A and D). The right ventricular diastolic pressure was also increased but less so, and the left atrial pressure greatly exceeded the right atrial pressure (Table I). Results of routine hematologic and biochemical investigations were normal.

An exploratory thoracotomy was performed to drain the pericardial effusion and to obtain a biopsy specimen. At operation, a large, lax pericardial effusion was found; the heart was only slightly enlarged, and the left ventricle felt abnormally firm. There was no reduction in the right or left atrial pressure after drainage of the pericardial effusion. A right atrial biopsy specimen was obtained and histologic studies revealed widespread replacement of the myocardium with amyloid and, in some areas, arteriolar deposition.

Postoperatively the patient manifested no improvement and he died 7 days later. Permission for postmortem examination was refused.

Case 2

A 53 year old man, previously well, presented with a 1 year history of progressive shortness of breath on exertion and more recent bilateral ankle edema. During the first half of 1973, several episodes of painless hematuria had been investigated at another hospital, but results of intravenous pyelograms and cystoscopy had been normal and the episodes had not recurred. Treatment for heart failure with digoxin and diuretic agents had brought about little improvement and he was transferred to Hammersmith Hospital for further investigation in January 1974.

Examination revealed a sick-looking man. Scattered pe-

TABLE I

Pressure and Volume Findings in Three Cases

	Pressures (mm Hg)					LV Volume (ml)				
Case no.	$\overline{RA}$	$\overline{PA}$	$\overline{PCW}$	RV (S/D)	LV S/Early D/ED	ES	ED	ED/m^2	EF (%)	CI
1	17	33	30	46/18	80/18/35	74	130	87	43	1.4
2	12	35	25	45/17	95/14/27	66	119	63	44	1.2
3	18	38	25	60/8	105/20/36	112	189	118	40	1.8
Normal values					2 10 ±7 ±2	25 ±10	. . .	70 ±25	70 ±4	2.5

CI = cardiac index (liters/min per m^2); D = diastolic; ED = end-diastolic; EF = ejection fraction; ES = end-systolic; LV = left ventricular; $\overline{PA}$ = mean pulmonary arterial; $\overline{PCW}$ = mean pulmonary capillary wedge; $\overline{RA}$ = mean right atrial; RV = right ventricular; S = systolic.

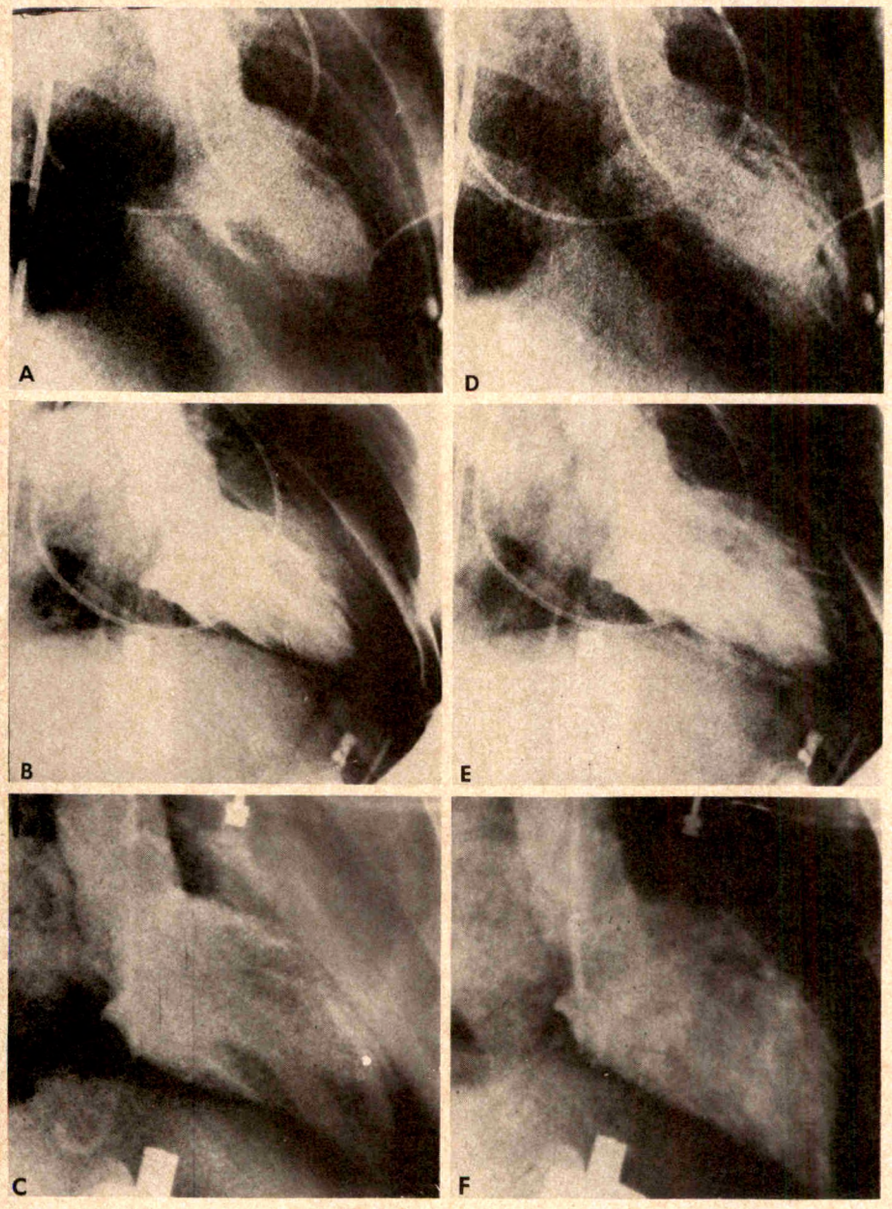


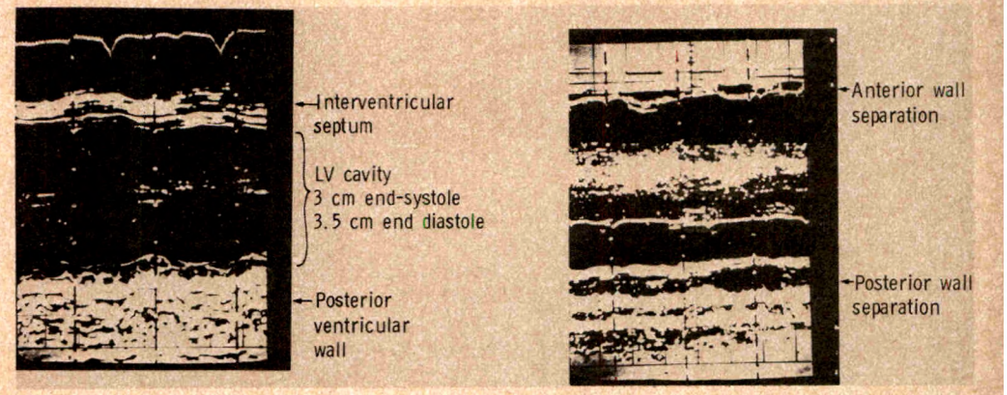
FIGURE 2. Left ventricular angiograms (full description in text) from Patients 1(**A** and **D**), 2(**B** and **E**) and 3(**C** and **F**). **A, B** and **C**, end-systole, showing normal shape but increased papillary muscle indentations and poor contraction. **D, E** and **F**, end-diastole, showing normal shape and shaggy outline.

techiae were observed over the base of the neck and forearms. The arterial pulse was regular, 96/min, and of small volume, with a blood pressure of 100/70 mm Hg. The jugular venous pressure was elevated 6 cm above the sternal angle. The cardiac impulse was difficult to locate. The heart sounds were faint with an intermittent third heart sound at the left sternal edge. A right pleural effusion was present. The liver was enlarged 4 cm below the right costal margin, tender but not pulsatile. No ascites was detected, but there was sacral and ankle edema.

A chest X-ray film (Fig. 1B) revealed an enlarged cardiac shadow with a large right pleural effusion. The electrocardiogram on admission disclosed complete atrioventricular (A-V) dissociation which reverted the next day to first degree A-V block after discontinuation of digoxin. The QRS voltage was low with small R waves in leads V_1 to V_3. Echocardiograms (Fig. 3) disclosed a normal-sized left ventricular diastolic dimension, reduced wall movement and a pericardial effusion. Cineangiographic studies confirmed that the left ventricle was not dilated but contracted poorly (Fig. 2, B and E). There was a sizable pericardial effusion lateral to the right atrial wall. As in Patient 1, the left-sided filling pressures were greatly elevated and exceeded those on the right side of the heart (Table I).

Laboratory values were: hemoglobin 16 g/100 ml, white blood cell count 10,100 mm^3, erythrocyte sedimentation rate 2 mm in 1 hour, and platelet count 138,000/mm^3. The only abnormal biochemical values were for bilirubin, 2.2 mg/100 ml, and alkaline phosphatase, 292 U/liter (normal 30 to 130 U/liter). Transaminase values were normal as were those for serum proteins and immunoglobulins; there was no Bence-Jones protein in the urine.

A rectal biopsy revealed amyloid deposition in the submucosa, small vessels of the lamina propria and in smooth muscle. Cardiac biopsy was not considered necessary, and cardiac amyloidosis was diagnosed on the basis of the he-



modynamic abnormality and the finding of amyloid on rectal biopsy. It was thought that the hematuria may have been due to amyloid deposition in the bladder mucosa. The patient had some symptomatic improvement after discontinuation of digoxin therapy, but the severe heart failure continued and he died at home. Autopsy was not performed.

Case 3

A 55 year old woman had IgA myelomatosis which had been diagnosed in 1968 and was well controlled with cyclophosphamide and corticosteroids. She was referred to Hammersmith Hospital in February 1974 because of an 8 month history of progressive dyspnea on exertion, orthopnea and ankle edema.

Examination revealed a fit-looking patient with no skin or mucosal abnormalities. The arterial pulse was 70/min and regular, with good volume. The blood pressure was 100/60 mm Hg. The jugular venous pressure was 10 cm above the sternal angle. The apex beat was diffuse and a faint third heart sound was heard. There was bilateral pleural effusion but no peripheral edema. The liver was enlarged 2 cm below the costal margin and was firm and tender with no ascites.

A chest X-ray film (Fig. 1C) revealed an enlarged cardiac shadow and severe heart failure. The electrocardiogram disclosed low voltage QRS complexes, first degree A-V block, small R waves in leads V_1 to V_3 and T wave inversion in leads V_5 and V_6. The echocardiogram revealed a normal left ventricular diastolic dimension and poor wall movement with increased systolic dimension. There was no pericardial effusion.

Results of hematologic investigations were normal, and the erythrocyte sedimentation rate was 16 mm in 1 hour. The total protein was 5.7 g/100 ml and albumin 410 g/100 ml; and there was a small M band in the A position of the protein strip. There was a large amount of Bence-Jones protein in the urine.

Endomyocardial biopsy was performed during cardiac catheterization, and histologic studies revealed extensive amyloid deposition in the interstitial tissue. The hemodynamic and left ventricular angiographic findings were similar to those in the other two patients (Table I, Fig. 2, C and F).

Hemodynamic and Angiographic Studies

Methods

The patients were premedicated with diazepam, 10 mg intramuscularly. Under local anesthesia, right heart catheterization was carried out from the right antecubital vein and left heart catheterization by the percutaneous femoral Seldinger approach. A modification of the method described by Brooksby et al.[2] was used. A 90 cm length of thin wall medical Teflon® tubing (Beckton and Dickinson, catalog no. 6412) flanged at one end was fitted over a no. 7F left ventriculographic catheter (Torcon, Cook). After passage of the guide wire and use of a no. 7F dilator, the catheter and sheath, which had been trimmed back so that its end lay proximal to the side holes of the catheter, were passed over the wire and into the femoral artery. The catheter and sheath were then advanced into the left ventricle. By gentle manipulation the catheter was then removed leaving the end of the sheath within the left ventricle. A no. 5F catheter-tip manometer (Millar Mikrotip) was then introduced through the sheath by way of a Y connector with "sealed" sidearm and pushed beyond the tip of the sheath into the left ventricle. Pressure recorded by catheter-tip manometer was calibrated to zero with fluid pressure recorded along the sheath. After pressure recordings, left ventricular cineangiocardiography was carried out in the right anterior oblique projection at a fixed tube height. Urografin 76, 50 ml, was injected at 10 ml/sec by a Contrac pump. Each pulsed cine exposure was recorded simultaneously with the left ventricular end-diastolic pressure recorded through a radiosensitive photoelectric cell in the X-ray beam. Link-up between cine filming and pressure recording was obtained using a battery-driven solenoid that recorded its own movement on the pressure tracing.[3]

Left ventricular volumes were calculated after the method of Kasser and Kennedy,[4] using electronic planimetry and calculation.[5] Plots of the instantaneous pressure volume relation through diastole were then constructed.[6]

Findings

Left ventricular cineangiography: The left ventricular angiographic appearances were characteristic and so similar in the three patients that a single description will suffice. In systole, ventricular contraction was greatly impaired with only slight visible reduction in volume. The normal chamber shape was retained and trabeculation was marked with prominent papillary muscles visible (Fig. 2, A, B and C). In diastole, the chamber size and shape were normal (Fig. 2, D, E and F). In two patients (Cases 1 and 2) coarsened trabeculation was also visible.

The left ventricular volumes were normal at end-diastole but above normal values at end-systole and the ejection fractions were low, 40 to 43 percent.

Hemodynamic data (Table I): All three patients had a very low cardiac output (index 1.2 to 1.8 liters/min per m^2).

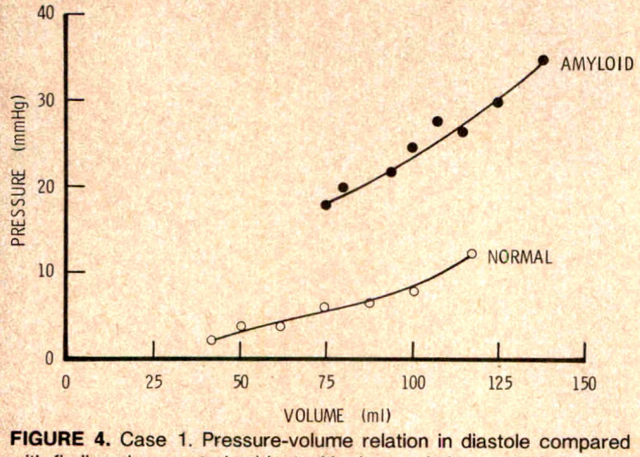


FIGURE 4. Case 1. Pressure-volume relation in diastole compared with findings in a control subject with chest pain but normal coronary arteries.

Right atrial and indirect left atrial pressures were both increased, but the left atrial pressure exceeded the right atrial pressure in each case and, similarly, the left ventricular end-diastolic pressures were greatly increased and exceeded the right ventricular end-diastolic pressures by at least 10 mm Hg in all three patients. The left ventricular pressure showed no diastolic "dip and plateau" but was high in early diastole and increased steadily toward end-diastole. A small atrial kick was visible in each case.

The abnormal diastolic pressure-volume relation of these stiff ventricles is illustrated in Figure 4. For each volume the pressure is greater than in the normal subject, and for each volume change the pressure change is greater than in the normal subject.

Discussion

The three cases illustrate the clinical, electrocardiographic, echocardiographic and hemodynamic features of functionally significant amyloid heart disease. The clinical features are well known, have been reviewed recently[7–9] and were exemplified in our patients. The echocardiographic, angiographic and hemodynamic findings have not been previously reported.

Refractory congestive cardiac failure is known to be the most common mode of presentation and dominated the clinical findings in our patients. Increased sensitivity to digitalis is a recognized[10] sign and occurred in Case 2. Pericardial effusion was seen in two of our patients and, although unstressed in published reports, the association with amyloid heart disease has been described previously[11] and was noted in isolated postmortem studies.[12,13] This finding is not surprising since amyloid may be deposited in both epicardium and pericardium.[14] In some cases the increased venous pressure may play a part in its pathogenesis. The heart may be of normal size or enlarged on X-ray film. It is possible that pericardial effusion was present in some reported cases of amyloid heart disease with cardiomegaly, but in its absence some of the cardiac enlargement may be explained by atrial dilatation, as in our Case 3. The atria are at high pressure and, being thin-walled, are more likely than the left ventricle to dilate even when infiltrated with amyloid.

The conduction system of the heart may be affected by amyloid deposits,[15] and the electrocardiographic abnormalities may suggest the diagnosis.[16–18] Low voltage QRS complexes, seen in all our cases, was the most common abnormal finding in most reported series.[19,20] Other abnormalities include atrioventricular and intraventricular conduction defects, as seen in our cases; small R waves in leads V_1 to V_4, simulating an anterior myocardial infarct; axis deviation; atrial fibrillation; atrial tachycardia with block; and premature ventricular contractions.

The echocardiographic abnormalities were characteristic (Fig. 3). They reflected the functional impairment and may provide a valuable clue to the underlying condition. Ultrasonic demonstration of a normal left ventricular dimension in diastole, diminished amplitude of excursion and increased systolic dimension are strongly suggestive of amyloid. Pericardial effusion may be revealed by ultrasound when the heart has erroneously been thought to be enlarged. Other myocardial disorders produce dissimilar echocardiographic abnormalities. In ischemic heart disease poor contraction is usually focal but, when more generalized, it leads to cavity dilatation as in congestive cardiomyopathy.

The cineangiographic appearance of the left ventricle was characteristic and should enable amyloid of the heart to be recognized. The trabeculae of the left ventricle were greatly coarsened. Papillary muscle impressions were marked, but there was no cavity distortion. Systolic emptying was reduced. The poor contractile function was reflected in the severely reduced ejection fraction which, in light of a normal end-diastolic volume, explains the very small pulse pressure and low cardiac output (Fig. 2).

Reduced left ventricular distensibility was demonstrated by the simultaneous measurements of volume and pressure in diastole (Fig. 4). Both early and end-diastolic pressures were elevated and the left ventricle was noncompliant; the ratio between change in pressure and change in volume ($\Delta p/\Delta v$) was greater than normal. This led to slow filling, which continued throughout diastole. A slow rate of ventricular filling is incompatible with a left ventricular source of a third heart sound. In our cases, the third heart sound was inconstant and heard best at the left sternal edge. When present in amyloid heart disease, the third heart sound probably arises from the right ventricle. The name "stiff heart" syndrome, based on the postmortem appearance, seems amply vindicated.[12]

Differentiation from constrictive pericarditis: The previously reported clinical resemblance of amyloid heart disease and constrictive pericarditis[21,22] was based on the typically increased venous pressure, unimpressive cardiac impulses and a moderate enlargement of the heart, often less than expected from the severity of the heart failure.[23] A hemodynamic similarity between the two conditions has also been

reported in studies[24–29] in which only right heart catheterization was performed.

The two conditions may indeed be contrasted. In constrictive pericarditis, there is nearly normal systolic emptying with a normal end-systolic volume and better maintenance of stroke output. Rapid filling early in diastole gives rise to an early third heart sound and there is little or no further filling late in diastole. A low early left ventricular diastolic pressure rises early to a plateau with a high mid- and end-diastolic pressure, and there is no atrial kick. The rapid ventricular filling gives the patient with constriction the ability to raise minute output by tachycardia. The right and left ventricular diastolic pressures are almost always similar in constrictive pericarditis,[29] another feature not found in our cases of amyloid heart disease.

Differentiation from other forms of cardiomyopathy: Functional distinction can be made between amyloid heart disease and other secondary heart muscle disorders as well as the primary heart muscle disorders (cardiomyopathies).[30] All known causes of heart muscle disorder result in impairment of the heart's contractile force. Myocardial fiber shortening is reduced, the residual volume increases and, except in cardiac amyloidosis, the cavities dilate. Systolic pump failure is probably the end result of many causes. When a cause cannot be established we designate it "dilated" (or congestive) cardiomyopathy. Alcohol, past hypertension or viral myocarditis may be invoked, but the end results are the same. The ventricular and atrial cavities progressively dilate but cardiac output is more or less maintained by the automatic compensation that dilatation provides as contraction fails. High filling pressures are readily reduced by diuretic agents without loss of stroke volume. Ventricular filling is fast with a low $\Delta p/\Delta v$ ratio over an abnormally great range of volume and, clinically, third heart sounds are characteristic.

In hypertrophic cardiomyopathy (idiopathic hypertrophic subaortic stenosis) there may be obstruction to left ventricular outflow when the abnormal muscle is confined mainly to the septum but emptying is achieved and the ejection fraction is high. When the free wall is also extensively involved, the main functional disorder is a diastolic abnormality that provides the main cause of death in this condition. Myocardial compliance is reduced, with an increased $\Delta p/\Delta v$ ratio, but the functional disorder differs from that caused by amyloid in the preservation of ejectile ability (except in some preterminal cases), the systolic deformity of the left ventricle and in the obstruction to outflow and mitral regurgitation when this is present.

Restrictive cardiomyopathy is the term given to the condition of a small group of patients who also have a diastolic disorder.[30,31] In this group systolic function is normal but diastolic filling is restricted. The heart is not enlarged. The third heart sound is early and loud. Simultaneous pressure and volume studies show that early filling of the left ventricle is rapid and the pressure is reduced but increases abruptly with cessation of further filling in mid- or later diastole. Unlike the patients with amyloid heart, these patients do indeed resemble patients with constrictive pericarditis very closely but can be recognized by the unequal involvement of the two ventricles in which the disease is seemingly often confined to the left side. Biopsy or autopsy reveals endocardial fibrosis. Most of these patients probably have endocardial disease, and the relation to Loeffler's disease of temperate zones and to endomyocardial fibrosis of the tropics has yet to be clarified.

Functional distinction from ischemic heart disease is also required. When coronary arterial occlusion has brought about sufficient loss of myocardial fibers for the heart to fail clinically, investigation invariably reveals a dilated left ventricle and the focal distribution of dyskinesia is nearly always apparent. In patients with angina who have not had an infarction, left ventricular function is normal except during pain. The increase in left ventricular diastolic pressure that precedes the development of anginal pain can be shown on angiography to be associated with the temporary development of focal dyskinesia causing an increase in diastolic and systolic volumes and a reduction in ejection fraction.

Acknowledgment

We thank Professor John F. Goodwin for kindly allowing us to study Patient 3 and Dr. Eckhardt G. J. Olsen for interpreting the biopsies. We thank Dr. Z. Asperger and Dr. Wiland Stone who kindly referred Patients 1 and 2 to us and gratefully acknowledge the help of Mrs. Phyllis Sym and Miss Diane Merry and their staffs in the laboratory studies and of Miss Rosemary Waterkeyn who typed the manuscript.

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Sinus Nodal Responses to Atrial Extrastimuli in Patients Without Apparent Sinus Node Disease

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In 36 patients without sinus node disease scanning with an atrial extrastimulus (A_2) was performed during sinus rhythm with the sinus cycle length measured in milliseconds. Zones of nonreset due to interference, reset, interpolation and sinus echoes were defined by noting the timing of the first response after A_2. Zones were defined in terms of their longest and shortest A_1-A_2 coupling intervals (in milliseconds). A zone of nonreset was found in 12 of 12 patients in whom A_2 was delivered late. The mean cycle length in these 12 patients was 779 msec, with a mean zone of nonreset of 779 to 585 msec (25 percent of cycle length). All 36 patients (100 percent) had a zone of reset. The mean cycle length in these 36 patients was 803 msec with a zone of reset from 692 to 319 msec (46 percent of cycle length). Seven of 36 patients (19 percent) had a zone of interpolation. The mean cycle length in these seven patients was 754 msec, with a mean zone of interpolation of 344 to 279 (9 percent of cycle length). Four of 36 patients (11 percent) had a zone of sinus echoes. The mean cycle length in these four patients was 870 msec, with a mean zone of echoes from 350 to 313 msec (4 percent of cycle length). Calculated sinoatrial conduction time ranged from 40 to 153 msec (mean $\pm$ standard deviation 92 $\pm$ 30 msec). Shortening of the cycle length with atrial pacing increased the number of patients with zones of interpolation and echoes.

In conclusion, zones of nonreset and reset are found in all patients with normal sinus nodal function, whereas zones of interpolation and echoes are much less common. Sinoatrial conduction time is surprisingly long in patients without apparent sinus node disease.

Sinus nodal function can be evaluated in patients with use of the atrial extrastimulus technique. However, available data concerning normal sinus nodal responses are limited. Goldreyer and Damato[1] demonstrated sinoatrial (S-A) entrance block (interpolation of the atrial extrastimulus) in 7 of 13 patients without sinus nodal dysfunction and suggested that this phenomenon was common. Narula et al.[2] reported similar interpolation of atrial extrastimuli in 7 of 28 patients with a normal sinus nodal recovery time and heart rate. Strauss et al.[3] studied five patients with sinus node disease and demonstrated clear-cut zones of nonreset due to interference in all patients and zones of sinus reset in four of five patients. In addition, they described an indirect method of calculating S-A conduction time utilizing the atrial extrastimulus technique. Childers et al.[4] demonstrated zones of sinus echoes and interpolation in intact canine hearts with use of the extrastimulus technique and described a patient with a similar sinus response. Paulay et al.[5] suggested that sinus nodal reentry occurred after atrial extrastimuli in 13 of 16 patients and proposed various mechanisms for this phenomenon.

In this study, we delineated sinus nodal responses in 36 patients without apparent sinus node disease. Zones of interference, reset, in-

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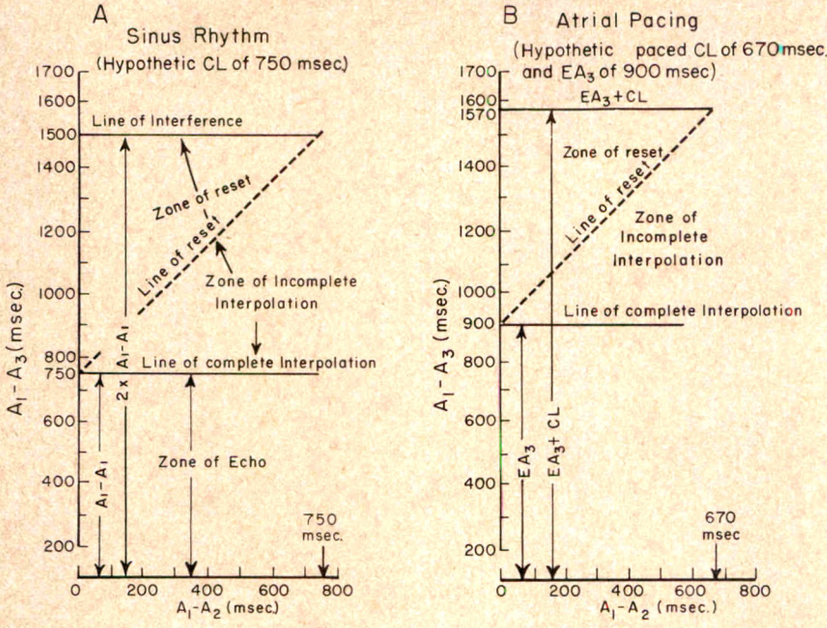

FIGURE 1. Graphic representation of sinus nodal responses to extrastimuli during sinus rhythm **(A)** and during atrial driving **(B)** at hypothetical cycle lengths (CL) of 750 and 670 msec, respectively. A_1-A_3 intervals **(ordinate)** are plotted as a function of A_1-A_2 intervals **(abscissa)** in msec. A_1-A_1 is the basic cycle length. EA_3 = expected first sinus response after A_2.

terpolation and echoes were quantitated. S-A conduction times were also calculated in all patients. Additional observations are presented concerning the effect on the various zones of pacing-induced changes in cycle length.

Materials and Methods

Material

The study group consisted of 36 patients who were studied during diagnostic hemodynamic or electrophysiologic cardiac catheterization. Criteria for patient selection included: (1) normal sinus rhythm with sinus rates between 60 and 100/min in all recorded resting electrocardiograms; (2) no suspicion of sinus node disease, either by history or electrocardiogram (specifically, recorded episodes of sinus arrest or sinoatrial block); (3) absence of premature atrial contractions or other documented atrial dysrhythmia; (4) normal atrial effective and functional refractory periods during electrophysiologic study[6]; and (5) normal sinus nodal recovery time.[7]

The mean age of the patients was 54 years (range 28 to 83); there were 29 men and 7 women. Three patients had no heart disease and 33 patients had organic heart disease (including 22 with intraventricular conduction disturbances).

Methods

The patients were studied in the resting, nonsedated and postabsorptive state. Informed consent was obtained. No patient was taking cardiac drugs at the time of study. Two electrode catheters were utilized for intracardiac recordings in the right heart chambers. The first (tripolar), passed percutaneously through a femoral vein and placed close to the tricuspid valve,[7] was used to record low right atrial and His bundle electrograms. The second (quadripolar) catheter was positioned at the junction of the superior vena cava and the right atrium. Two of the poles of this catheter were utilized for atrial stimulation and the other two poles for recording high right atrial electrograms. Simultaneous electrocardiographic leads I, II, III and V_1 were also recorded. Recordings were obtained on a multichannel oscilloscopic recorder (Electronics for Medicine, DR-16) at paper speeds of 100 and 200 mm/sec. Stimuli were approximately twice diastolic threshold, 2.5 msec in duration and delivered by a programmable digital stimulator (M. Bloom, Philadelphia). Sinus nodal recovery time was defined as previously described, as were the measurements of atrial effective and functional refractory periods.[6–8]

The premature atrial stimuli were introduced in diastole during spontaneous sinus rhythm and also at one atrial-driven cycle length shorter than the sinus cycle length. The mean cycle length was 803 msec during sinus rhythm and 645 msec during atrial driving. Atrial extrastimuli were delivered after every eighth beat (spontaneous or driven) at progressively decreasing coupling intervals (in 5 or 10 msec increments) until atrial capture was lost. In 12 patients, the whole range of sinus cycle length was scanned; in the re-

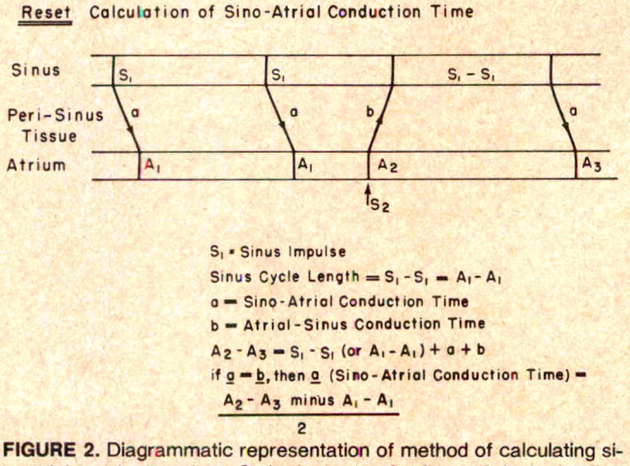

FIGURE 2. Diagrammatic representation of method of calculating sinoatrial conduction time. S_2 is the extrastimulus and A_3 is the first spontaneous sinus response after S_2.

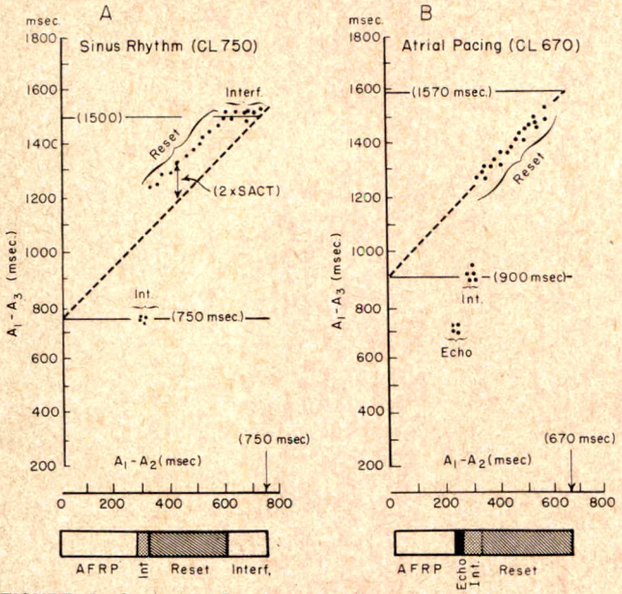

FIGURE 3. Case 12. Graphic representation of sinus nodal responses and zones. **A**, during sinus rhythm at a cycle length (CL) of 750 msec. The zone of interference (Interf.) ranges from 750 to 600 msec. The zone of reset is between 590 and 320 msec and the zone of interpolation (Int.) is from 310 to 290 msec. The interval between the group of points during reset and line of reset represents the conduction time in and out of the sinus node (2 × sinoatrial conduction time [SACT]). The atrial functional refractory period (AFRP) is 290 msec. **B**, during atrial pacing at a cycle length (CL) of 670 msec. Sinus nodal recovery time (EA_3) at this rate is 900 msec. The zone of interference is abolished. The zone of reset is between 650 and 330 msec. The zone of interpolation ranges from 320 and 280 msec. There is development of a sinus echo zone from 270 to 230 msec. The atrial functional refractory period is decreased to 230 msec. The zones are depicted at the bottom of each panel.

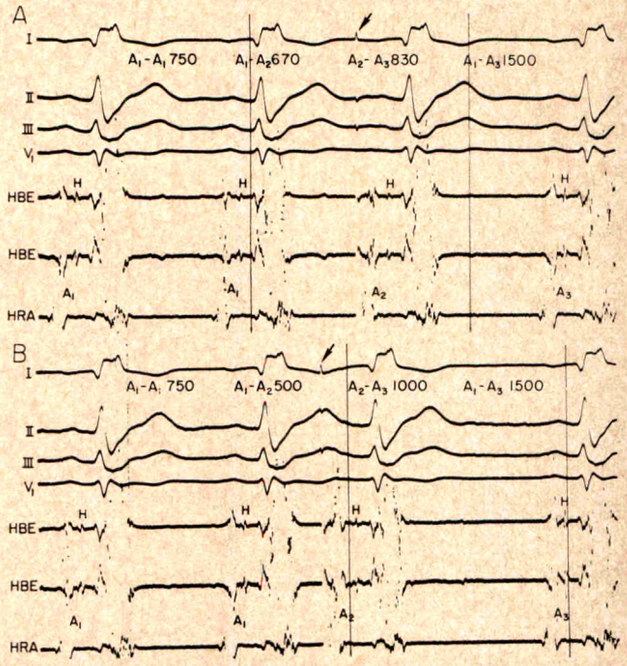

FIGURE 4. Case 29. Demonstration of interference responses. In each panel, simultaneous electrocardiographic leads I, II, III, V_1, His bundle electrogram (HBE) and high right atrial electrogram (HRA) are shown. Paper speed is 100 mm/sec and time lines are at 1 second intervals in this and subsequent illustrations. The extrastimulus is labeled with an **arrow** and the His bundle potential as H. A_1, A_2 and A_3 are defined in the text. **A**, sinus rhythm at a cycle length (CL) of 750 (A_1-A_1) msec. A_2 is elicited at a coupling interval (A_1-A_2) of 670 msec. A_3 occurs at an A_2-A_3 interval of 830 msec; thus A_1-A_3 is equal to 2 × A_1-A_1 (670 + 830 = 1500 msec). **B**, decrease in the A_1-A_2 interval to 500 msec results in lengthening of the A_2-A_3 interval to 1000 msec. The A_1-A_3 interval remains constant at 1,500 msec (2 × A_1-A_1).

maining 24 patients, scanning was begun at prematurity equivalent to approximately 80 percent of the sinus cycle. The stimuli, electrograms and intervals used were designated as follows:

1. *During sinus rhythm:* A_1 was the high right atrial electrogram of the spontaneous sinus beat. S_2 was the extrastimulus and A_2 was the high right atrial electrogram in response to S_2. A_3 was the first spontaneous sinus response after S_2 (and A_2). The A_1-A_1 interval was the sinus cycle length and A_1-A_2 was the measured atrial coupling interval in response to S_2. This interval was equal to A_1-S_2 plus atrial latency. A_1-A_3 was the interval between the last spontaneous sinus response (A_1) and the first response after A_2.

2. *During atrial driving:* S_1 and A_1 were the driving stimulus and high right atrial electrogram, respectively, of driven beats. S_2 was the extrastimulus and A_2 was the high right atrial electrogram in response to S_2. A_3 was the first sinus response after A_2. A_1-A_2 and A_1-A_3 were defined as during sinus rhythm. Expected A_3 (EA_3) was defined as the mean of three sinus nodal recovery times at the driven cycle length (S_1-S_1).

Analysis of Results

During Sinus Rhythm

A simplified method of data presentation and analysis was used (Fig. 1A). For each patient, A_1-A_3 responses were plotted (ordinate) against A_1-A_2 coupling intervals (abscissa). Additional reference lines were derived on the graph as follows:

1. *Line of interference:* This line was parallel to the abscissa at an interval (on the ordinate) equal to two times the sinus cycle length (A_1-A_1). A_3 responses falling on this line were termed sinus interference (nonreset), implying that A_2 collided with the emerging sinus impulse in the perisinus tissue and failed to discharge the sinus node.

2. *Line of interpolation:* This line was parallel to the abscissa at an interval (on the ordinate) equal to one sinus cycle length (A_1-A_1). A_3 responses falling on this line suggested that A_2 was totally interpolated (unidirectional sinus block).

3. *Line of reset:* This line of identity intersected the lines of interference and interpolation. It intersected the former at an A_1-A_2 interval equal to sinus cycle length (A_1-A_1) and the latter at an A_1-A_2 interval equal to 0. A_3 responses on this line were reset responses with a calculated sinoatrial conduction time of 0 msec (see calculation of sinoatrial conduction time described later).

Zones of response: With use of this method of data presentation, four zones of sinus responses could be determined. The various zones were defined in accord with previous physiologic definitions.[1–5] In each patient, a zone could be described in terms of its longest and shortest A_1-A_2 coupling intervals and also in terms of its absolute duration. When all patients with a given zone were being considered, the zone could be described in terms of mean

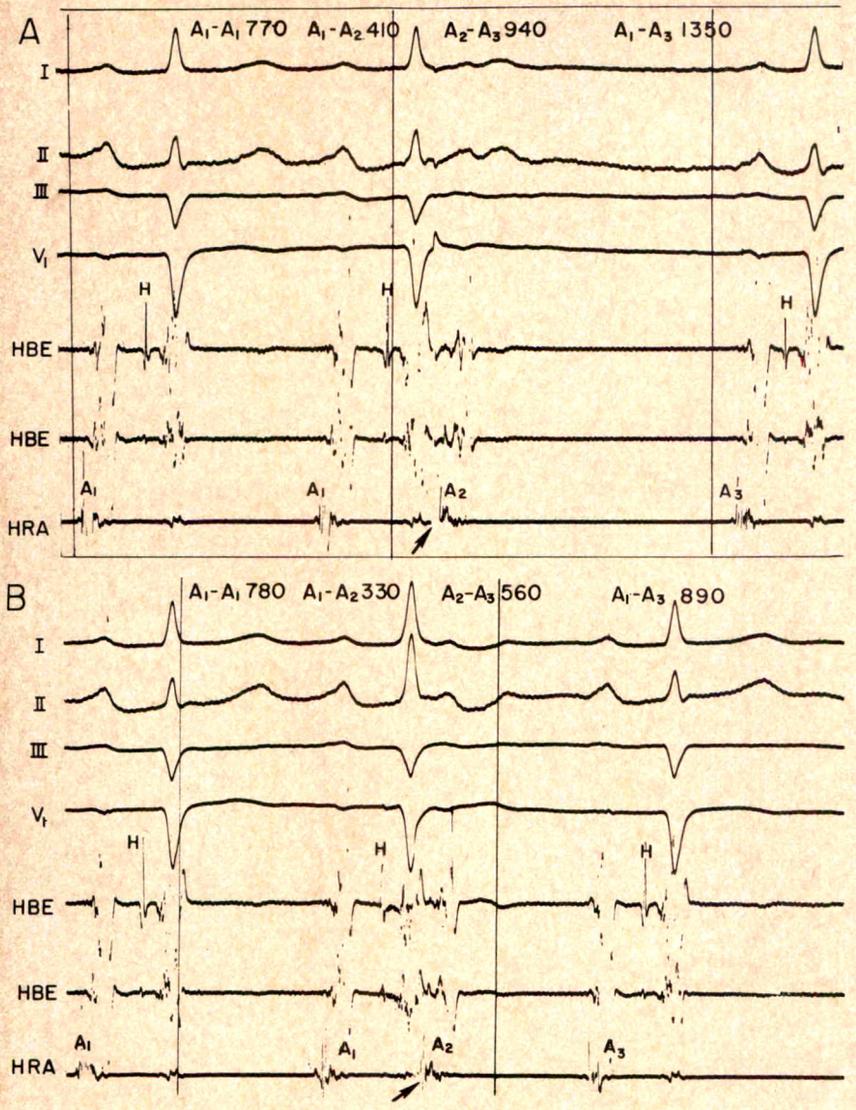

FIGURE 5. Case 10. Demonstration of sinus reset **(A)** and incomplete interpolation **(B). A,** sinus rhythm at a cycle length (CL) of 770 (A_1-A_1) msec. A_2 is elicited at an A_1-A_2 interval of 410 msec. The A_2-A_3 interval of 940 msec is more than A_1-A_1, whereas A_1-A_3 (1,350 msec) is less than twice A_1-A_1. The sinus node is reset by A_2. The sinoatrial conduction time can be calculated by noting the difference between A_2-A_3 (940 msec) and A_1-A_1 (770 msec) and dividing by 2. **B**, a decrease in the A_1-A_2 interval to 330 msec resulted in shortening of the A_2-A_3 interval to 560 msec (less than A_1-A_1). The A_1-A_3 interval of 890 msec is more than A_1-A_1. This A_3 response is incomplete interpolation (see text).

longest and shortest A_1-A_2 coupling intervals as well as mean absolute duration.

The four zones were as follows (Fig. 1A):

1. *Zone of interference:* A_3 responses falling on the line of interference defined this zone. This occurred when the A_1-A_3 interval equaled twice the A_1-A_1 interval despite a decreasing A_1-A_2 interval.

2. *Zone of reset:* A_3 responses falling between the line of interference and the line of reset defined this zone. In this zone, the A_1-A_3 interval decreased linearly as the A_1-A_2 interval decreased, and responses were generally parallel and slightly above the line of reset.

3. *Zone of interpolation:* A_3 responses falling on the line of interpolation defined the zone of complete interpolation (A_1-A_3 equal to A_1-A_1). A_3 responses falling between the line of interpolation and the line of reset defined a zone of incomplete interpolation (A_1-A_3 more than A_1-A_1 and A_2-A_3 less than A_1-A_1). For purposes of analysis, zones of complete and incomplete interpolation were grouped together.

4. *Zone of sinus echoes:* A_3 responses falling below the line of interpolation defined this zone. For a diagnosis of sinus echo, the P wave configuration of A_3 had to approximate that of the normal P wave, and there had to be a high to low sequence of atrial depolarization.

Sinoatrial (S-A) conduction time: S-A conduction time, calculated by the method of Strauss et al.[3] (Fig. 2), was obtained by measuring the difference between the A_2-A_3 interval during reset and the A_1-A_1 interval, and dividing by 2. In each patient S-A conduction times were calculated for each A_1-A_2 interval producing reset and these were averaged to a mean value. S-A conduction time could also be roughly calculated from the graph by measuring half the distance between the points defining the zone of reset and the line of reset (Fig. 1A and 3A).

During Atrial Driving (Fig. 1B)

During atrial pacing, A_1-A_3 responses were again plotted against A_1-A_2 coupling intervals, but the line of interpolation was the expected A_3 (EA_3). The line of reset was the line of identity drawn from the intersection of the line of interpolation with the ordinate. This line would intersect a theoretical line drawn parallel to the abscissa with an A_1-A_3 interval equal to EA_3 plus the paced cycle length being studied, at an A_1-A_2 coupling interval equal to the S_1-S_1 interval. Zones of reset, interpolation and echoes

were defined as before. A zone of interference could not be defined during atrial driving.

Results

During Sinus Rhythm (Table I)

Sinus interference (Fig. 3 and 4): A zone of interference was defined in all of the 12 patients in whom S_2 was delivered late in the sinus cycle. The mean zone of interference in these 12 patients was between 779 and 585 msec (absolute value 194 msec) at a mean sinus cycle length of 779 msec (in these 12 patients). In these patients, the zone of interference accounted for the last 25 percent of the total cycle length (A_1-A_1).

Sinus reset (Fig. 3, 5A and 6A): Sinus reset was defined in all 36 patients (100 percent). In all patients, A_3 responses during reset formed a line parallel to the line of reset, suggesting that sinus automaticity was constant. The mean zone of sinus reset in the 36 patients was between 692 and 319 msec (absolute value 373 msec) at a mean cycle length of 803 msec and accounted for 46 percent of the total cycle length. The outer limit of the zone was either the inner limit of the zone of interference (in 12 patients) or the longest A_1-A_2 interval tested (in 24 patients). The true outer limit of the zone of reset is presumably somewhat longer than the cited value of 692 msec since, in 24 patients, stimulation was begun at prematurity equivalent to approximately 80 percent of the sinus cycle. Hence, the reset zone is probably slightly longer than that given. The inner border of the zone of reset was either the atrial functional refractory period or the outer limit of either the zone of interpolation or zone of echoes.

Sinus interpolation (Fig. 3, 5B and 7): Sinus interpolation (total or partial) was defined in 7 of 36 patients (19 percent). In these patients, the development of partial or total interpolation occurred abruptly at a critical A_1-A_2 coupling interval. The mean zone of interpolation in these seven patients was between 344 and 279 msec (absolute value 65 msec) at a mean cycle length of 754 msec (in these seven patients) and accounted for 9 percent of the latter. The outer limit of this zone was the inner limit of the reset zone. The inner limit of the zone of interpolation was the atrial functional refractory period.

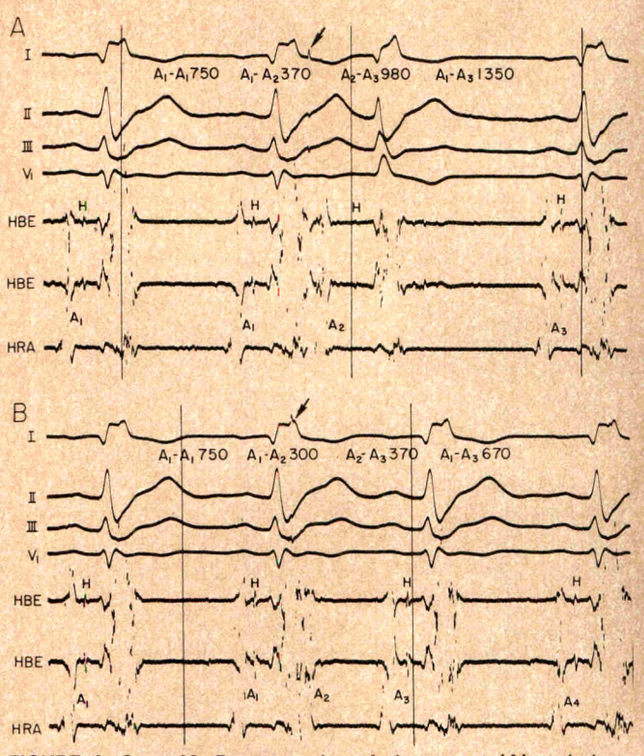

FIGURE 6. Case 29. Demonstration of sinus reset **(A)** and sinus echo **(B). A,** sinus rhythm at an A_1-A_1 interval of 750 msec. At an A_1-A_2 interval of 370 msec, the sinus node is reset. **B,** a decrease in the A_1-A_2 interval to 300 msec results in abrupt shortening of the A_2-A_3 interval to 370 msec. An A_1-A_3 interval of 670 msec is less than A_1-A_1. The P wave configuration of A_3 is identical to that of the sinus P wave, and a high to low sequence of atrial depolarization is maintained.

Sinus echoes (Fig. 3 and 6B): Sinus echo zones were defined in 4 of 36 patients (11 percent). In these patients, the onset of the echo zone was always abrupt at a critical A_1-A_2 coupling interval. The mean zone of sinus echoes in these patients ranged from 350 to 313 msec (absolute value 37 msec) at a mean cycle length of 870 msec and accounted for 4 percent of the total cycle length duration (in these four patients). The outer limit of this zone was always the inner limit of the zone of reset, whereas the inner limit was always the atrial functional refractory period. Sustained sinus reentrant tachycardia was not noted in the four patients with sinus echo zones.

TABLE I

Zones of Sinus Responses During Sinus Rhythm (CL_1) and Atrial Pacing (CL_2) (average mean values)

	Interference		Reset		Interpolation		Echo	
	CL_1	CL_2	CL_1	CL_2	CL_1	CL_2	CL_1	CL_2
Patients								
Number	12	. . .	36	36	7	22	4	8
Percent	100	. . .	100	100	19	61	11	22
Mean CL (msec)	779	. . .	803	645	754	648	870	621
Mean zone (msec)	779–585	. . .	692–319	614–354	344–279	392–265	350–313	329–248
Absolute value (msec)	194	. . .	373	260	65	127	37	81
Percent of CL	25	. . .	46	40	9	20	4	13

CL = cycle length.

Calculated sinoatrial conduction time: The S-A conduction time was calculated during sinus reset responses (Fig. 2). Calculated S-A conduction time in the 36 patients was 92 ± 30 msec (mean ± standard deviation) and ranged from 40 to 153 msec. As mentioned, there was a linear decrease of the A_1-A_3 interval with progressive shortening of the A_1-A_2 interval during reset, and all these responses fell in a straight line parallel to the line of reset (line of zero S-A conduction time), suggesting that sinus automaticity was not changing during reset.

During Atrial Driving

Shortening of the cycle length by atrial pacing resulted in the following changes (Table I, Fig. 3B):

Sinus reset: This was present in all the patients as the initial response during atrial driving. The mean zone of reset was 614 to 354 msec at a mean cycle length of 645 msec (absolute value 260 msec) and accounted for 40 percent of the total cycle scanned (S_1-S_1). The outer limit of this zone was the longest A_1-A_2 interval tested. (In some patients, the longest A_1-A_2 interval tested was slightly shorter than the A_1-A_1 interval.) The inner limit of this zone was either the atrial functional refractory period or the outer limit of the zone of interpolation or zone of echoes. The absolute zone of the reset decreased with atrial pacing because of shortening of the A_1-A_1 interval (decreasing the outer limit) and also because of encroachment of interpolation or sinus echo zones (increasing the inner limit).

Sinus interpolation: Shortening of the cycle length resulted in the following effects on interpolation responses: In two of the seven patients with interpolation during sinus rhythm, interpolation was abolished. In the remaining five patients with interpolation during sinus rhythm, the absolute zones of interpolation were increased. Seventeen additional patients manifested interpolation during atrial driving. The mean zone of interpolation in the 22 patients with interpolation during atrial driving was 392 to 265 msec (absolute value 127 msec) at a mean cycle length of 648 msec and accounted for 20 percent of the total paced cycle length duration (S_1-S_1) in these 22 patients.

Sinus echoes: In one of four patients with echoes during sinus rhythm, the echoes were abolished. In the remaining three patients, absolute zones of sinus echoes were increased. Sinus echoes occurred in five additional patients upon shortening of the cycle length with pacing. The mean zone of sinus echoes in all eight patients with echo zones during atrial driving was 329 to 248 msec (absolute value 81 msec) at a mean cycle length of 621 msec and accounted for 13 percent of the total paced cycle length.

Atrial functional refractory period: The functional refractory period of the atrium was measured in all patients during sinus rhythm and atrial driving (mean cycle length 803 and 645 msec, respectively). The atrial functional refractory period during sinus rhythm was 299 ± 5.3 msec (mean ± standard error of the mean) and 250 ± 7.5 msec during atrial pacing ($P < 0.01$).

Discussion

Sinus nodal function after premature atrial depolarization (S_2): It has previously been shown in both animals and man that atrial premature depolarizations (S_2) exert variable effects on atrial rhythm.[1–5,9–14] Microelectrode studies in rabbits by Bonke et al.[9] demonstrated that an extrastimulus (S_2) lengthened the succeeding sinus cycle and that this lengthening was directly proportional to the degree of prematurity of S_2 within certain limits. The asystolic pause (A_2-A_3) after S_2 increased progressively with a progressive increase in prematurity of S_2 up to approximately 70 percent of the sinus cycle. This temporary depression of S-A nodal pacemaker automaticity was demonstrated to be due to depression of diastolic depolarization. In other experimental studies Han et al.[10] and Bonke et al.[11] demonstrated that as S_2 was elicited early in the sinus cycle (A_1-A_1), the A_2-A_3 interval shortened because of either interpolation or echo phenomenon. Sinoatrial entrance block and slow conduction of early S_2 impulses within the perisinus nodal tissue (or even the shift of pacemaker site within the S-A node) were suggested as possible explanations of these respective sinus responses.

Strauss and Bigger[12] demonstrated in rabbit hearts

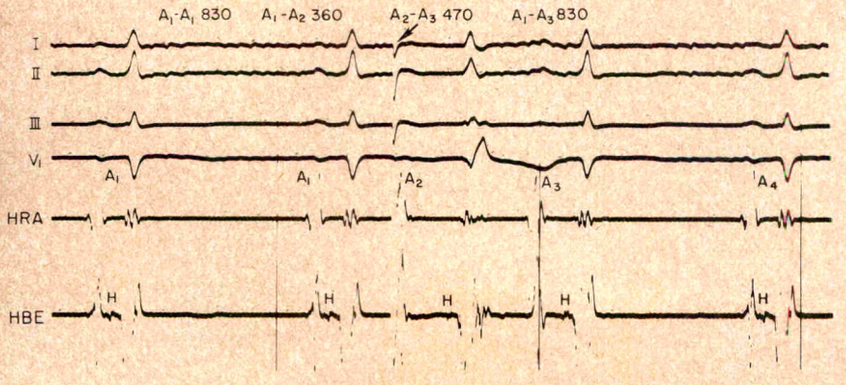

FIGURE 7. Case 28. Demonstration of complete interpolation. The A_1-A_1 interval is 830 msec. At an A_1-A_2 interval of 360 msec, the A_3 occurs at an A_1-A_3 interval of 830, which is equal to A_1-A_1. The P wave configuration of A_3 approximates that of the sinus P wave and a high to low sequence of atrial depolarization is maintained. The A_3-A_4 interval is equal to A_1-A_1. The QRS complex following A_2 is of right bundle branch block configuration as a result of aberrant conduction.

the presence of a perinodal junctional zone with characteristic electrophysiologic properties between the S-A node and surrounding atrial tissue. They suggested that this zone served as the site of normal conduction delay for impulses entering and leaving the sinus node. They also concluded that premature atrial stimuli, elicited late or very early in the sinus cycle, did not gain entrance to the sinus node through this transition zone because of either interference (late stimuli) or refractoriness (early stimuli). Premature stimuli elicited in the middle of the sinus cycle gained access to the S-A node after traversing the zone and reset the sinus.

Childers et al.[4] demonstrated in dogs that sinus nodal responses after S_2 could be categorized into zones defined by the longest and shortest A_1-A_2 intervals giving rise to a particular response. They described zones of interpolation and sinus echoes after extrastimuli. Canine studies by Paulay et al.[13] demonstrated the occurrence of repetitive sinus echoes after an early elicited S_2. Klein et al.[14] observed four basic patterns of alteration in the S-A nodal rhythm after S_2 in rabbits. They termed these responses type IV (when S_2 initiated very late in the sinus cycle failed to affect the S-A node); type III (when S_2 elicited during the middle of A_1-A_1 depolarized the S-A node); and types II and I (when S_2 initiated early in A_1-A_1 resulted in S-A nodal interpolation and echoes).

Variable sinus responses to S_2 (depending upon its degree of prematurity) were reported by Narula et al.[2] in some patients. They observed the progressive lengthening of the A_2-A_3 interval with shortening of the A_1-A_2 interval when A_2 was elicited late in the sinus cycle. With increasing prematurity of A_2, interpolation and sinus reentry responses were also noted. The incidence rate of interpolation was 26 percent (7 of their 28 patients) in patients with normal sinus rates. Goldreyer and Damato[1] reported S-A nodal entrance block (complete interpolation) in 6 of 13 patients (46 percent) without sinus nodal dysfunction. This was observed when S_2 was elicited with a prematurity equal to 30 to 40 percent of the A_1-A_1 interval. Strauss et al.[3] evaluated five patients with symptomatic sinus node disease. They demonstrated zones of nonreset due to interference (when S_2 fell in the last 20 percent of the A_1-A_1 interval) and zones of reset. They also reported an indirect means of calculating S-A conduction time; the latter ranged from 68 to 156 msec in their four patients with sinus node disease.

Zone of interference after an extrastimulus: This study presents a systematic evaluation of sinus nodal function and characterizes sinus nodal responses after an extrastimulus in a large number of patients without apparent sinus node disease. Zones of interference were defined in all of the patients (12 of 12) in whom S_2 was delivered late in the sinus cycle, thus suggesting that the interference response would have been present in all 36 patients if S_2 had been delivered late enough. This zone of interference should theoretically be present in all patients, since there should be a zone in late diastole in which the incoming impulse collides with the outgoing impulse and thus cannot reach and reset the sinus node. This zone of interference should approximate twice the sinoatrial conduction time (assuming equal antegrade and retrograde conduction times in and out of the sinus node). In this study, the zone of interference (in the 12 patients) accounted for approximately 25 percent of the total sinus cycle length. This observation is consistent with the previous report of Strauss et al.,[3] who described a 20 percent zone of interference in four patients with sinus node disease. In one of their patients, interference accounted for 100 percent of the scanned sinus cycle. However, they termed this a "zone of nonreset." The term "zone of interference" seems preferable since nonreset could apply to any response that is not reset such as interpolation and echo.

Zone of reset: Reset was demonstrated in all the patients in this series compared with the 80 percent incidence rate reported by Strauss et al.[3] in five patients with sinus node disease. The absence of reset in one of their five patients was believed to reflect advanced sinoatrial disease. Increasing prematurity of S_2 in our patients did not result in further prolongation of A_2-A_3, the later intervals remaining relatively constant. This suggested that (1) S-A nodal automaticity did not change; (2) there was no shift of pacemaker site; and (3) antegrade and retrograde conduction to the sinus node remained constant during the zone of reset. As mentioned previously, the true zone of reset in our patients is presumably slightly longer than reported since in 24 of our patients the scanning was started at prematurity equivalent to about 80 percent of the sinus cycle.

Zone of interpolation: Interpolation was found in 19 percent of our patients compared with incidence rates of 46 and 26 percent reported, respectively, by Goldreyer and Damato[1] and Narula et al.[2] This response occurred when S_2 was initiated with prematurity equal to or less than 50 percent of the sinus cycle, suggesting that A_2 was occurring during the absolute entrance refractory period of the sinus node. The actual site of S-A entrance block was probably in the perinodal fibers.[12] It is assumed that with complete interpolation S_2 neither resets the sinus node nor affects the S-A conduction time of A_3. During partial interpolation, it is assumed that S_2 does not reset the sinus node but does prolong the S-A conduction time of A_3 because of concealed conduction to the perinodal fibers.[4,11]

Sinus echo zones: These were the least common responses in our study (11 percent of patients), in contrast to the frequent demonstration of sinus echo zones during animal experiments and in another study involving man.[4,5,13,14] Our patients with sinus echoes had no history of atrial tachycardia and none manifested sustained sinus reentrant tachycardia

during the study. The early appearance of A_3 (sinus echo) is thought to be due not to accelerated automaticity of the sinus node but to increased refractoriness of perinodal fibers.[4,9,11,13] It is suggested that A_2 arrives at this perinodal region during its relative refractory period, is blocked at one front, enters at another site and then slowly conducts in this region until the neighboring atrial tissue recovers, allowing exit and reexcitation of the atrium. Paulay et al.[13] showed that crushing the sinus node in dogs resulted in disappearance of sinus echoes, thereby suggesting that the actual site of turnaround or reentry may be the sinus node itself.

S-A conduction tissue: The ability to measure S-A conduction time with use of the extrastimulus technique in patients was reported by Strauss et al.[3] The sinus responses (A_2-A_3) during the zone of reset usually exceeded that of the A_1-A_1 interval. These workers suggested that the degree to which the A_2-A_3 interval exceeded the A_1-A_1 interval reflected the time for retrograde conduction of the S_2 into the S-A node and for antegrade conduction of the first returning S-A nodal beat (A_3). If one assumes that antegrade and retrograde conduction times were of equal duration, the S-A conduction time would be half the difference of A_2-A_3 and A_1-A_1. The similarity between S-A nodal conduction times in our patients and those of five patients with sinus node disease described by Strauss et al.[3] may have partially reflected the presence of subclinical perisinus or sinus node disease in our patients, since most of our patients had organic heart disease. However, none of our patients had apparent sinus nodal dysfunction, and it is conceivable that the range of S-A conduction times reported in our series of 36 patients reflects the normal range for this measurement. We did not believe it justified to submit a large number of normal healthy patients to right heart catheterization in order to define normal sinus nodal responses.

Effect of cycle length: There are no data available in man regarding the effect of a decrease in cycle length on the S-A nodal responses. The interference responses were totally abolished with atrial pacing because of continuous suppression of the sinus node. The zone of reset was contracted because of the decrease in the A_1-A_1 interval (which is a result of method and not a physiologic response) and because of encroachment due to lengthened zones of interpolation and sinus echoes. The development of or increase in zones of interpolation and echoes in our patients reflected both an increase in the outer limits of these zones and a decrease in the inner limits. The increase in the outer limit of these zones probably reflected an increase in absolute and relative refractoriness of perinodal fibers with a decrease in cycle length. The decrease in the inner limits reflected a decrease of atrial functional refractory period exposing perinodal fibers to impulses at shorter coupling intervals (A_1-A_2).

Clinical implication: Sinus interference and reset responses to the atrial extrastimulus technique were universally present in the 36 patients, whereas interpolation and echoes were much less common. S-A conduction time was 92 ± 30 msec (mean ± standard deviation). Shortening of the cycle length markedly facilitated sinus nodal reentry and interpolation. Since these studies were performed in patients without apparent sinus node disease, the responses observed characterize the functional properties of the normal S-A conduction system in man. Whether similar studies will be useful for evaluation of sinus node disease deserves further prospective study in a large number of patients with suspected sinus nodal dysfunction.

Acknowledgment

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Nitroglycerin in Experimental Myocardial Infarction

Effects on Regional Left Ventricular Length and Tension

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Controversy has existed concerning the value of nitroglycerin therapy in acute myocardial infarction. With use of Walton-Brodie strain gauge arches and mercury-in-Silastic segment length gauges, the effects of nitroglycerin (30 μg/kg intravenously) were studied on local tension and length characteristics of the ischemic, border and nonischemic zones of the left ventricle in 10 open chest dogs. In the nonischemic zone total tension increased to 144.8 ± 13.6 (mean ± standard error of the mean) percent ($P < 0.005$) of control levels, and segment length decreased to 79.4 ± 4.4 percent ($P < 0.01$) with infusion of nitroglycerin 15 to 30 minutes after coronary ligation. Changes were similar in the groups given nitroglycerin 45 to 60 minutes and 2 to 3 hours after ligation. The border zone exhibited an increase in total tension to 132.3 ± 8.4 percent ($P < 0.005$) of control level and a decrease in segment length to 79.0 ± 2.4 percent ($P < 0.001$) in the 15 to 30 minute group. In the 45 to 60 minute group, tension increased to 117.9 ± 4.8 percent ($P < 0.005$), whereas length decreased to 86.8 ± 1.4 percent ($P < 0.001$); and in the 2 to 3 hour group tension increased to 124.9 ± 6.0 percent ($P < 0.005$), and length decreased to 91.9 ± 3.5 percent ($P < 0.001$). The decrease in magnitude of responsiveness in the 45 to 60 minute and 2 to 3 hour postligation groups compared with the 15 to 30 minute postligation group was highly significant ($P < 0.005$). The central ischemic zone showed no significant change in tension or length in any group. Maximal response to nitroglycerin administration in both tension and length parameters was observed within 30 to 60 seconds and was concomitant with a decrease in systolic pressure to 73.3 ± 1.9 percent ($P < 0.001$) and an increase in heart rate to 107.2 ± 1.0 percent.

Nitroglycerin improves the contractile performance of the nonischemic and border zones after coronary occlusion without affecting the central ischemic zone. However, the border zone exhibits a progressive decrease in contractile response as a function of time. These data suggest that nitroglycerin has the overall effect of functionally reducing the extent of the ischemic area and strongly supports its potential clinical usefulness in acute myocardial infarction.

The use of nitroglycerin in acute myocardial infarction has become controversial. The traditional view that this agent is contraindicated in acute myocardial infarction[1] has been challenged by experimental findings that it decreases the ischemic injury[2] and has a reflex positive inotropic effect.[3] In addition, recent clinical studies have indicated that nitroglycerin is of benefit in patients with left ventricular dysfunction and pulmonary edema,[4] and that it considerably improves cardiac performance in patients with myocardial infarction of less than 15 hours' duration.[5] In patients with left ventricular dysfunction due to chronic coronary disease, ventriculographic studies from our laboratory[6–8] have shown that nitroglycerin differentiates reversible from irreversible contraction abnormalities.

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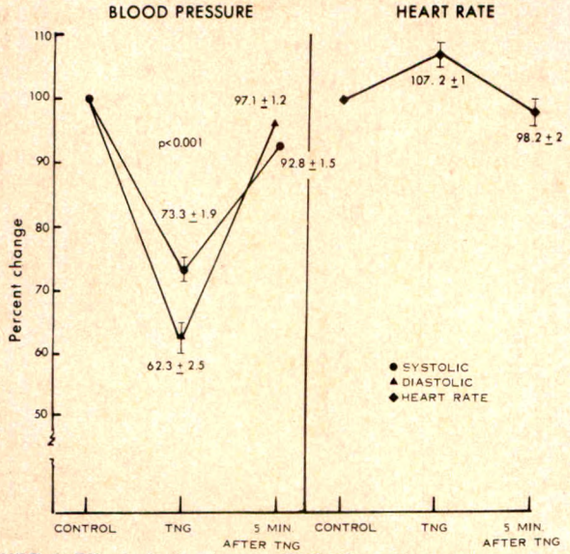

FIGURE 1. Effect of nitroglycerin (TNG) (30 μg/kg intravenously) on blood pressure and heart rate.

The precise manner in which nitroglycerin affects the regional contraction characteristics of the left ventricle under circumstances of ischemia and infarction is unknown. This experimental study was therefore undertaken to examine the effects of nitroglycerin on length and tension relations of ischemic, border and nonischemic ventricular zones after acute coronary occlusion.

Material and Methods

Experiments were performed on 10 mongrel dogs weighing 25 to 30 kg and anesthetized intravenously with sodium pentobarbital (30 mg/kg). Under intermittent positive pressure respiration, a thoracotomy was performed with a midsternal incision. The heart was supported in a pericardial cradle. A polyethylene tube was introduced through an external jugular vein for intravenous infusion. Central aortic pressure was monitored with use of a P23Db transducer through a wide bore stiff catheter introduced by way of a common carotid artery.

The left anterior descending coronary artery was isolated 3 cm distal to its origin. Local electrograms from the potentially ischemic, border and nonischemic zones were recorded by inserting three pairs of fine Teflon®-coated stainless steel wires, one in each zone. Transient ischemia was produced by obstructing the left anterior descending coronary artery momentarily and local electrograms were recorded to define the central ischemic, border and nonischemic areas. The ischemic zone showed marked S-T segment elevation whereas the border zone exhibited S-T segment depression and T wave inversions (similar to a zone of "injury"). No S-T segment or T wave changes were observed in the normal zone. The coronary occlusion was released immediately and the heart allowed to recover for 10 minutes. Local electrograms invariably returned to control level in this period. Three Walton-Brodie strain gauge arches of 120 ohm resistance with adjustable feet were fixed with deep sutures in the ischemic, border and nonischemic zones.[9] The myocardial segment under the two feet of each strain gauge arch was stretched by 30 percent of its initial length. The rate of tension rise (dT/dt) was measured using a linear resistance-capacitance differentiating circuit.[9,10]

A mercury-in-Silastic® tubing segment length gauge[9,11] ranging in length from 1.5 to 2 cm was sutured adjacent and parallel to the strain gauge in each zone to monitor concurrent changes in segment length. Standard lead II of the electrocardiogram was monitored throughout each experiment. All records were taken simultaneously on a multichannel oscilloscopic recorder at a paper speed of 100 mm/sec.

After control recordings of simultaneous segment tension and length were taken, the coronary artery was ligated. A bolus injection of nitroglycerin (30 μg/kg) was infused intravenously at variable intervals of 15, 30 and 45 minutes and 1, 2 and 3 hours after coronary ligation. In any single study, a minimal interval of 45 minutes between any two nitroglycerin interventions was allowed, at which time the changes in blood pressure and the heart rate produced by nitroglycerin had returned to control values.

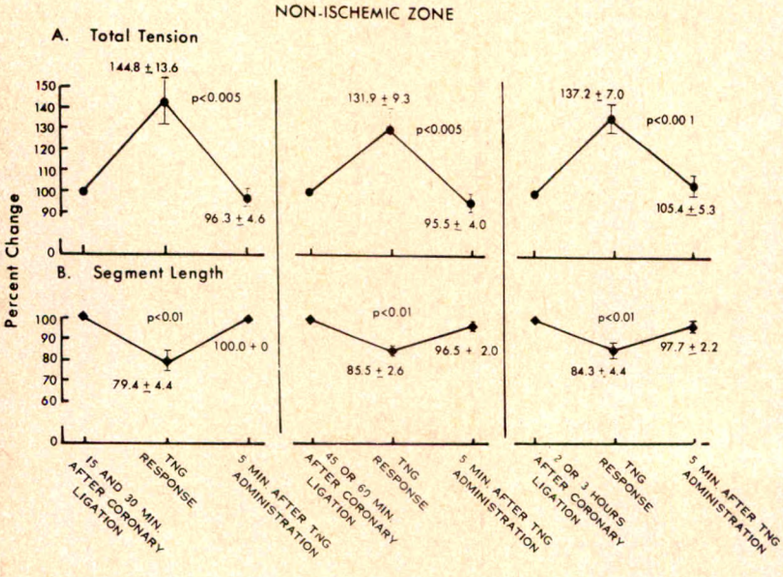

FIGURE 2. Effect of nitroglycerin (TNG) on total tension **(A)** and segment length **(B)** in the nonischemic zone at 15 to 30 minutes, 45 to 60 minutes and 2 to 3 hours after coronary ligation.

Studies were divided into three groups: administration of nitroglycerin at 15 or 30 minutes after ligation, at 45 or 60 minutes after coronary ligation and at 2 or 3 hours after coronary occlusion.

Tension and segment length recordings were made before and immediately after coronary occlusion, immediately before the administration of nitroglycerin, continuously for 5 minutes after the nitroglycerin infusion and every 2 to 5 minutes for 45 minutes after the nitroglycerin intervention. The following indexes[9,11,12] were measured and interpreted as percent change from values immediately before administration of nitroglycerin (1) preejection tension (2) ejection tension (3) total tension (4) rate of tension rise (dT/dt), and (5) phasic segment length. Statistical analysis was performed by Student's *t* test for paired values.

At the end of each experiment, 2 cc of methylene blue dye was injected into the left anterior descending coronary artery immediately distal to the site of occlusion to ascertain the area of left ventricular myocardium it subserved and to confirm that the gauges were placed correctly in each zone.

Results

The changes in segment length and tension development in the ischemic, border and nonischemic ventricular zones after coronary arterial ligation have been described previously.[9] Briefly, in the ischemic zone the preejection tension decreases to 59.2 ± 8.0 percent of control level (P <0.001) and the rate of tension rise (dT/dt) decreases to 45.3 ± 8.3 percent (P <0.001) within the first 15 minutes of coronary ligation followed by a more gradual decline up to 4 hours in duration.[9] Ejection tension falls precipitously, developing a negative slope that returns to zero after 30 to 60 minutes of ligation. Segment length increases to 238.0 percent (P <0.001) in the first 15 to 30 minutes and then declines to 105.0 percent of control level after 4 hours of ligation. The border zone shows a decrease in tension and increase in length similar to the reductions in the ischemic zone but the changes are of considerably less magnitude, whereas ejection tension in the border zones does not show a negative slope. The nonischemic zone shows no significant changes.[9]

Effect of nitroglycerin on blood pressure and heart rate: Figure 1 illustrates the effect on blood pressure and heart rate with each intravenous injection of nitroglycerin. The systolic blood pressure decreases significantly (P <0.001) to 73.3 ± 1.9 percent of control level and the diastolic pressure decreases to 62.3 ± 2.5 percent. Five minutes after the nitroglycerin injection, both the systolic and the diastolic blood pressures return to near control level (Fig. 1). The heart rate increases insignificantly to 107.2 ± 1.0 percent of the control value and within 5 minutes of nitroglycerin administration returns to 98.2 ± 2.0 percent.

Effect of nitroglycerin on nonischemic zone: Figure 2 illustrates the changes in total tension and segment length in the three groups of experiments. Total tension (Fig. 2A) increases to 144.8 ± 13.6 percent of control level (P <0.005) with nitroglycerin infusion 15 to 30 minutes after coronary occlusion and returns to control level in 5 minutes. In the 45 to 60 minute and 2 to 3 hour groups, nitroglycerin produces similar increases in total tension and, when the three groups are compared, no statistical difference in the magnitude of tension changes produced is demonstrable (Fig. 2A). The rate of tension rise (dT/dt) increases to 138.2 ± 16.6 percent in the 15 to 30 minute group, 124.2 ± 8.0 percent in the 45 to 60 minute group and 132.9 ± 9.6 percent in the 2 to 3 hour group (P <0.005). Preejection tension increases to 141.8 ± 26.6 percent (P <0.02), 132.2 ± 24.9 percent (P <0.02) and 131.2 ± 12.1 percent (P <0.02), respectively, in the three groups. Ejection tension exhibits an increase to 153.9 ± 19.5 percent (P <0.01) in the 15 to 30 minute group, 146.7 ± 10.5 percent (P <0.001) in the 45 to 60 minute group and 134.0 ± 7.8 percent (P <0.001) in the 2 to 3 hour group.

Segment length (Fig. 2B) decreases to 79.4 ± 4.4 percent of control level (P <0.01) in the 15 to 30 minute group. In the 45 to 60 minute group, it decreases to 85.5 ± 2.6 percent (P <0.01) and in the 2 to 3 hour group, declines to 84.3 ± 4.4 percent (P <0.01). There was no statistical difference in the magnitude of reductions in segment length among the three groups (Fig. 2B).

Effect of nitroglycerin on the border zone: Immediately after nitroglycerin infusion, the border

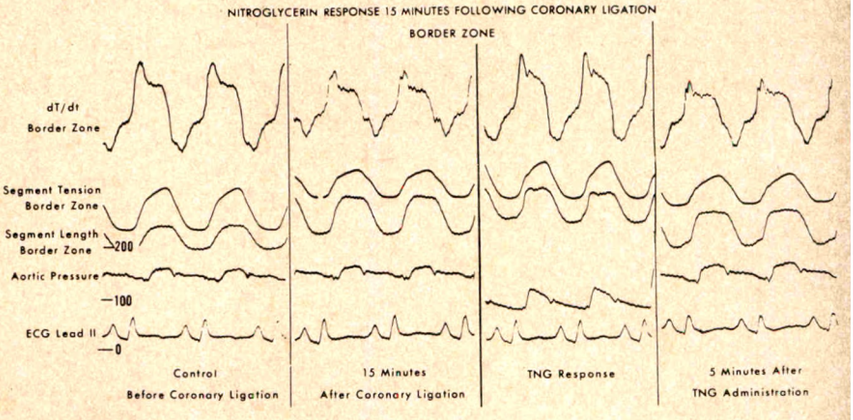

FIGURE 3. A typical experiment demonstrating the effect of intravenous administration of nitroglycerin on tension and length recordings from the border zone after 15 minutes of coronary ligation. Coronary ligation produces a decrease in tension as well as its rate of rise (dT/dt) and an increase in segment length. Nitroglycerin infusion (TNG response) produces a significant increase in tension and dT/dt and a decrease in segment length concomitant with the decrease in blood pressure. With the return of blood pressure to control level, both tension and segment length revert to the level before nitroglycerin.

zone exhibits a significant increase in tension and decrease in length concomitant with the decrease in blood pressure (Fig. 3). These changes occur within 15 to 30 seconds of nitroglycerin administration (Fig. 4). Five minutes after the nitroglycerin infusion both total tension and segment length return to pre-nitroglycerin levels. Figure 5 compares the changes in total tension and segment length of the border zone in the three groups of experiments. In the 15 to 30 minute group, total tension increases to 132.3 ± 8.4 percent of control level (P <0.005) and returns to 98.6 ± 4.8 percent 5 minutes after nitroglycerin infusion (Fig. 5A). In the 45 to 60 minute group, it increases to 117.9 ± 4.8 percent of control level (P <0.005) and returns to 104.1 ± 5.4 percent. In the group with 2 to 3 hours of occlusion, total tension similarly increases to 124.9 ± 6.0 percent (P <0.005) and returns to control level 5 minutes after nitroglycerin administration. The increase in total tension in the 15 to 30 minute group is significantly higher (P <0.005) than that in the groups with 45 to 60 minutes or 2 to 3 hours of coronary occlusion. The rate of tension rise also shows a significant increase to 154.6 ± 10.5 percent in the 15 to 30 minute group, 141.9 ± 9.8 percent in the 45 to 60 minute group and 129.7 ± 4.5 percent in the 2 to 3 hour group. The magnitude of the increase in dT/dt in the 15 to 30 minute group is significantly higher (P <0.005) than that in the 45 to 60 minute or the 2 to 3 hour groups. Other tension measurements such as preejection and ejection tension exhibit changes similar to those observed in total tension and rate of tension rise. Preejection tension increases to 154.2 ± 18.2 percent (P <0.01) in the 15 to 30 minute, 119.8 ± 10.7 percent in the 45 to 60 minute and 116.5 ± 11.8 percent in the 2 to 3 hour groups, respectively. Ejection tension shows an increase to 138.5 ± 14.7 percent (P <0.02) in the 15 to 30 minute, 123.0 ± 8.2 percent (P <0.02) in the 45 to 60 minute and 138.6 ± 9.2 percent (P <0.001) in the 2 to 3 hour groups.

Concomitant with the decrease in blood pressure, segment length decreases to 79.0 ± 2.4 percent (P <0.001) in the 15 to 30 minute group and returns to control level within 5 minutes of nitroglycerin infu-

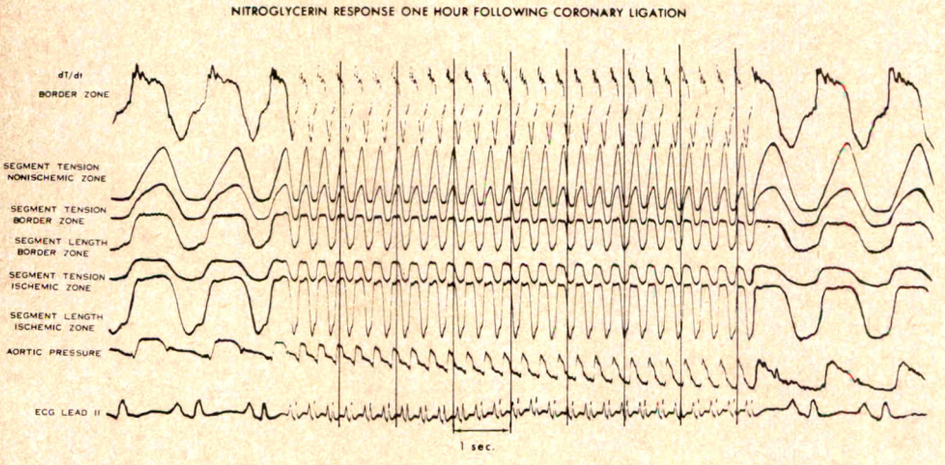

FIGURE 4. A continuous recording of tension and length from the nonischemic, border and ischemic left ventricular zones after 60 minutes of coronary ligation demonstrating the rapidity of response in nonischemic and border zones concomitant with change in blood pressure. Time lines 1.0 sec.

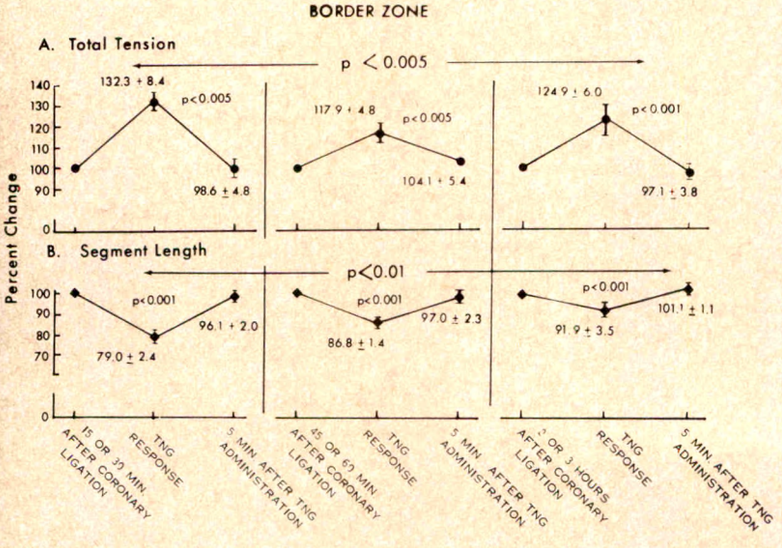

FIGURE 5. Effect of nitroglycerin (TNG) on total tension **(A)** and segment length **(B)** in the border zone at 15 to 30 minutes, 45 to 60 minutes and 2 to 3 hours after coronary ligation.

sion (Fig. 5B). In the 45 to 60 minute group, segment length decreases to 86.8 ± 1.4 percent (P <0.001). In the 2 to 3 hour group, segment length decreases only to 91.9 ± 3.5 percent of control level (P <0.001). When the three groups are compared, the decrease in segment length in the 15 to 30 minute group is significantly greater (P <0.01) than that in the 45 to 60 minute group or the 2 to 3 hour group.

Effect of nitroglycerin on the ischemic zone: Nitroglycerin had no significant effect on total tension or segment length in the ischemic zone (Fig. 6 and 7). The rate of tension rise, preejection tension and ejection tension did not reveal any significant changes.

Discussion

Nitroglycerin has been shown to increase cardiac output and left ventricular stroke work index in patients with acute myocardial infarction and heart failure[4] as well as in those with chronic coronary heart disease.[13] However, the effects of the drug in patients without heart failure are not uniform.[3,14] The differential effects of nitroglycerin on the local performance of the ischemic, border and nonischemic left ventricular zones after coronary arterial ligation have not been systematically examined. Recent studies from our laboratory have indicated that after acute coronary occlusion there is a rapid decline in tension and an increase in segment length of the ischemic zone of the left ventricle in the first 15 minutes followed by a gradual decline in both indexes over a period of 4 hours.[9] The border zone shows changes similar to the ischemic zone but of lesser magnitude, while the nonischemic zone is essentially unaffected.[9] The results of this study indicate that nitroglycerin has a differential effect on these three left ventricular zones. The nonischemic zone shows a significant contractile improvement manifested by increase in tension and decrease in length when nitroglycerin is administered from 15 minutes to 3 hours after coronary occlusion (Fig. 2). The border zone shows qualitatively similar changes (Fig. 3), although of decreasing magnitude as a function of time after coronary occlusion (Fig. 5). In contrast, the ischemic zone is relatively unaffected by the nitroglycerin infusion (Fig. 6 and 7). The decreasing magnitude of responsiveness in the border zone suggests that, over the observed period of coronary occlusion, the degree of ischemic injury increases and the contractile ability of the area therefore progressively deteriorates.

Recent ventriculographic studies in coronary artery disease have shown that nitroglycerin administration improves contractile ability of some asynergic segments while others remain unresponsive.[6–8] The

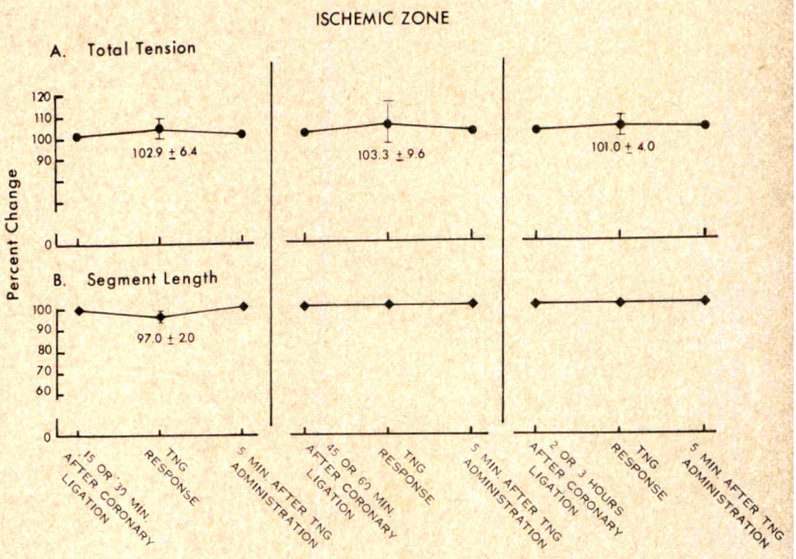

FIGURE 6. Effect of nitroglycerin (TNG) on total tension **(A)** and segment length **(B)** in the ischemic zone at 15 to 30 minutes, 45 to 60 minutes and 2 to 3 hours after coronary ligation.

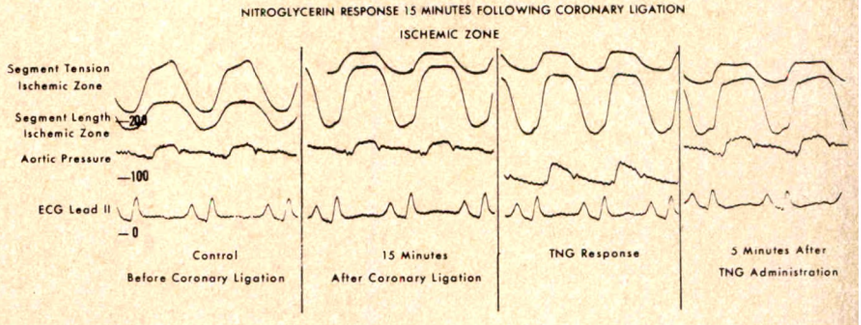

FIGURE 7. A typical experiment demonstrating the effect of intravenous administration of nitroglycerin on tension and length recordings from the central ischemic zone after 15 minutes of coronary ligation. Coronary ligation causes a marked decrease in tension and increase in segment length. Nitroglycerin infusion (TNG response) produces a significant decrease in blood pressure but no change in tension and length recordings (contrast with the same recordings from the border zone in Figure 3).

responsiveness of the asynergic zones presumably depends upon the improvement in balance between their oxygen supply and demand induced by nitroglycerin.[8] Our study, when taken in that context, suggests that only areas that have residual contractile ability, such as the border zones, show improvement in contractile performance whereas zones with frank infarction are relatively unresponsive.

Mechanism of nitroglycerin effects on contractility: The mechanism of these changes produced by administration of nitroglycerin is conjectural. The dramatic increase in tension and decrease in length of the border and nonischemic zones occurring concomitantly with the decrease in blood pressure suggests that these effects are produced by a decrease in afterload. The latter results in decreased myocardial oxygen consumption and thus improves the balance between oxygen supply and demand.[15] If the border zone consists of ischemic but viable myocardium, an improvement in oxygen balance should cause improvement in its contraction. These findings are consistent with the observation that nitroglycerin reduces the ischemic injury.[2] Another mechanism may relate to an increase in coronary blood flow to the affected left ventricular zone after nitroglycerin administration.[16] However, since these changes are transient and regress when the blood pressure returns to control level, the mechanism related to afterload appears more logical. Nitroglycerin has also been shown to have a positive inotropic sympathetic reflex effect, which may play a partial role.[3]

Role of blood pressure: It has been observed that a decrease in blood pressure may cause a concomitant decrease in coronary blood flow and thus increase the extent of ischemic injury.[1,2] In this study, nitroglycerin infusion was so regulated that the level of systolic blood pressure was not allowed to fall below 90 mm Hg and the diastolic pressure remained in the range of 60 to 70 mm Hg. Previous studies on the effect of blood pressure on contractile force measured by the Walton-Brodie strain gauge arch indicate that contractile force may increase with significant increases in systolic or diastolic pressure.[12] In the present study the increase in tension was observed concomitantly with a decrease in systolic and diastolic blood pressure. It is thus clear that the contractile changes recorded by the strain gauge are not only the effect of the change in blood pressure. This is further substantiated by the differential changes in the three zones of the left ventricle studied. Similarly, the changes in heart rate were not of sufficient magnitude (Fig. 1) to cause alterations in the strain gauge measurements.[17]

Clinical implications: If these data are applicable to man, the findings suggest that, after nitroglycerin administration, the nonischemic and marginally affected areas of the left ventricle improve their contractile behavior over a 3 hour period following coronary occlusion whereas the central ischemic area is relatively unaffected. This has the overall effect of functionally reducing the extent of the ischemic area and thereby improving overall left ventricular performance. In the context of other experimental studies that indicate that nitroglycerin decreases ischemia and enzyme release[2] and of clinical studies demonstrating improved function,[4,5] our study strongly supports the potential clinical usefulness of nitroglycerin in cases of acute myocardial infarction.

Acknowledgment

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Dissociation of the Inotropic Effect of Digitalis From Its Effect on Atrioventricular Conduction

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The relation between sequential changes in left ventricular contractility and atrioventricular (A-V) nodal conduction and refractoriness was assessed in open chest dogs during intravenous administration of acetylstrophanthidin (5 μg/kg) at 5 minute intervals until toxic arrhythmias developed. At each time interval, high fidelity left ventricular pressure, its electronic derivative (dP/dt) and a His bundle electrogram were simultaneously recorded and the A-V nodal refractory period was measured by graded trains of stimuli. Animals were studied with an intact autonomic state (Group I), with pharmacologic blockade of both the beta adrenergic and parasympathetic system (Group II) and with parasympathetic blockade (Group III). Whereas contractility increased in response to small doses of digitalis, displaying a linear dose-response relation independent of autonomic tone, A-V nodal transmission indexes responded minimally to less than 50 percent of the toxic dose of digitalis, and the response was dependent upon autonomic tone. These results indicate a dissociation between the effects of digitalis on contractility and A-V transmission in that the major drug action on the ventricular contractile mechanism is a direct, linear one in contrast to the nonlinear response of A-V nodal transmission, which is predominantly mediated through the autonomic system. Clinically, these observations imply that the optimal dose and serum level of digitalis required to treat congestive heart failure may differ significantly from those required to treat supraventricular tachycardias, the therapeutic response of the latter being largely determined by the underlying autonomic tone.

From the Krannert Institute of Cardiology, the Department of Medicine, Indiana University School of Medicine, and the Veterans Administration Hospital, Indianapolis, Ind. This study was supported in part by the Herman C. Krannert Fund, Indianapolis, Ind.; Grants HL-060308, HL-05363 and HL-05749 from the National Heart and Lung Institute, National Institutes of Health, Bethesda, Md; and the Indiana Heart Association, Indianapolis, Ind. Manuscript accepted December 27, 1974.

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In clinical practice, digitalis is used for two important pharmacologic actions: (1) to augment inotropic state, especially in depressed myocardium; and (2) to slow atrioventricular (A-V) conduction and prolong A-V refractory period in order to treat supraventricular tachyarrhythmias. Although the effects of digitalis on myocardial contractility[1–5] and A-V nodal conduction and refractoriness[6–11] have been extensively studied in the past, little is known of the comparative changes in these two variables as a function of the dose-related response.[12]

The objective of this study was to quantitate simultaneously sequential changes in left ventricular contractility and A-V nodal conduction and refractoriness. Since the actions of digitalis may be either direct, or indirect, as a consequence of the interaction of digitalis with the autonomic system,[13] the experiments were conducted in the setting of variable, but defined autonomic tone.

Methods

Preparation

Eighteen mongrel dogs, weighing 14 to 24 kg, were anesthetized with pentobarbital alone or in combination with morphine sulfate (see later) and were

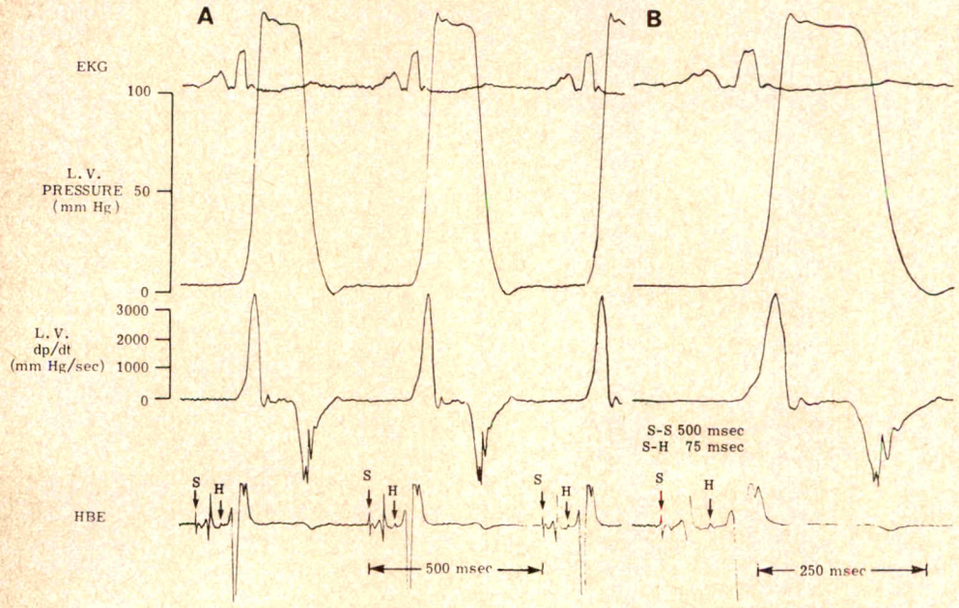

FIGURE 1. Simultaneous tracings of the electrocardiogram (EKG), left ventricular (L.V.) pressure, its first derivative (L.V. dp/dt) and the His bundle electrogram (HBE) at a basic cycle length (S-S) of 500 msec. H = His bundle potential; S = atrial pacing impulse. **A**, paper speed of 100 mm/sec. **B**, paper speed of 200 mm/sec.

ventilated by a Harvard respiratory pump. Rectal temperature was continuously monitored; the range of variation was within 1.5° C. The heart was exposed through a right thoracotomy and suspended in a pericardial cradle. A micromanometer-tip catheter (Mikro-Tip Pressure Transducer, model pc-350, Millar Instruments, Houston, Texas) was positioned in the left ventricular cavity by retrograde catheterization from the carotid artery. A tripolar catheter was introduced into the right femoral vein and positioned across the tricuspid valve for recording of the His bundle electrogram.[14] For atrial pacing, a stainless steel electrode was anchored to a fixed position near the A-V node in the right atrial wall.

High fidelity left ventricular pressure was recorded from the micromanometer-tip catheter. The first derivative of the left ventricular pressure pulse (dP/dt) was obtained by an analog derivative circuit that provides an amplitude that is a linear function of frequency with an error of less than 3 percent for frequencies to 400 hertz. Atrial pacing was accomplished by a digital stimulator (Digipulser, W.P. Instruments, Inc., Hamden, Conn.) set to deliver square impulses 2 msec in duration at 4 milliamperes. The signal from the tripolar catheter for His bundle recording was applied to an alternating current coupled differential amplifier with a selected frequency response of 40 to 500 hertz.

Experimental Groups

Control group (pentobarbital alone): Three dogs were anesthetized with pentobarbital alone without additional pharmacologic intervention. Anesthesia was achieved by an initial intravenous injection of pentobarbital, 30 mg/kg body weight, and maintained by supplemental doses of 1.5 to 2.0 mg/kg administered every 30 minutes. This regimen was adopted because preliminary experiments showed the regimen to produce hemodynamically stable preparations with a constant level of anesthesia.

Group I—animals without autonomic blockade: In five animals anesthesia was accomplished with intramuscularly administered morphine sulfate, 2.5 mg/kg, followed in 30 minutes by intravenously administered pentobarbital, 15 mg/kg, to preserve parasympathetic tone.[15]

Group II—animals with autonomic blockade: To establish combined parasympathetic and beta adrenergic blockade, five animals were given atropine, 0.05 mg/kg, and dl-propranolol (Inderal®), 0.2 mg/kg intravenously.[16] No intervention was given to block alpha adrenergic receptors, and anesthesia was accomplished as in the control animals.

Group III—animals with parasympathetic blockade: In five animals, atropine, 0.05 mg/kg, was injected to produce effective parasympathetic blockade. The mode of anesthesia was the same as in the control animals.

Experimental Procedures (Digitalis Administration)

After completion of all cannulations the sinoatrial node was crushed with clamps and the heart constantly paced by the right atrial stimulating electrode at a basic cycle length of 500 msec. After appropriate pharmacologic autonomic blockade according to protocol for the various animal groups, acetylstrophanthidin*, 5 μg/kg body weight, was administered intravenously over 30 seconds at 5 minute intervals until toxic arrhythmias developed. The dose of acetylstrophanthidin was chosen after a preliminary study showed it to produce toxic arrhythmias in approximately 1 hour. The onset of toxic arrhythmias was defined as the appearance of ventricular premature beats in salvos of three or more, ventricular tachycardia, sustained ventricular bigeminy, or junctional tachycardia.

At the end of each 5 minute interval, the respirator was discontinued during the postexpiratory phase and left ventricular pressure, its first derivative (dP/dt), the bipolar His electrogram and a standard lead II electrocardiogram were simultaneously recorded on a multichannel direct-writing light beam oscillograph (Visicorder, model 1108, Honeywell) at a paper speed of 200 mm/sec (Fig. 1). After this maneuver, the respirator was turned on and the A-V nodal refractory period was determined as described later. Throughout the study period, all tracings were continuously displayed on oscilloscopic screens.

* Supplied by Dr. G. C. Chiu, Eli Lilly and Co., Indianapolis, Ind.

TABLE I

Sequential Changes in Left Ventricular Contractility and Atrioventricular Nodal Transmission During Acetylstrophanthidin Infusion (mean ± standard error of the mean)

	Percent Subtoxic Dose of Acetylstrophanthidin						
	Control	25%	50%	75%	100%	F	*P*
Group I. ANS Intact (no. = 5)							
dP/dt max (mm Hg/sec)	2,192 ± 180	2,525 ± 215	3,094 ± 273	3,249 ± 359	3,573 ± 344	17.08	<0.001
dP/dt-40 (mm Hg/sec)	1,737 ± 95	2,009 ± 143	2,309 ± 205	2,497 ± 314	2,609 ± 331	10.12	<0.005
S-H (msec)	95 ± 5	96 ± 6	97 ± 6	101 ± 7	103 ± 7	1.32	NS
AVRP (msec)	190 ± 3	194 ± 5	195 ± 5	205 ± 5	212 ± 9	10.11	<0.005
Group II. ANS Blockade (no. = 5)							
dP/dt max (mm Hg/sec)	1,512 ± 125	1,925 ± 202	2,350 ± 276	2,792 ± 327	3,345 ± 394	29.83	<0.001
dP/dt-40 (mm Hg/sec)	1,342 ± 104	1,663 ± 156	1,994 ± 203	2,319 ± 200	2,689 ± 247	36.35	<0.001
S-H (msec)	111 ± 4	110 ± 4	106 ± 1	107 ± 1	111 ± 3	0.15	NS
AVRP (msec)	254 ± 16	246 ± 18	239 ± 17	246 ± 16	256 ± 13	0.01	NS
Group III. PNS Blockade (no. = 5)							
dP/dt max (mm Hg /sec)	3,131 ± 363	3,397 ± 384	3,646 ± 464	4,271 ± 418	4,607 ± 337	10.62	<0.005
dP/dt-40 (mm Hg/sec)	2,317 ± 132	2,622 ± 179	2,832 ± 191	3,152 ± 189	3,429 ± 207	26.35	<0.001
S-H (msec)	89 ± 4	90 ± 5	90 ± 5	91 ± 5	92 ± 5	0.23	NS
AVRP (msec)	180 ± 3	187 ± 4	187 ± 4	194 ± 2	204 ± 5	21.55	<0.001

ANS = autonomic nervous system; AVRP = atrioventricular nodal refractory period; dP/dt max = maximal dP/dt; dP/dt-40 = dP/dt at 40 mm Hg of left ventricular pressure; F = significance of linear regression coefficient; no. = number of dogs; NS = not significant; *P* = probability; PNS = parasympathetic nervous system; S-H = atrial stimulus to His potential time.

Definitions

dP/dt max: Maximal dP/dt. This variable was averaged from three or four consecutive cardiac cycles at the postexpiratory quiescent phase.

dP/dt-40: The dP/dt at 40 mm Hg of left ventricular pressure.[17]

S-H time: The interval between the atrial stimulus (S) and the first rapid deflection (H) of the bipolar His electrogram. S-H time approximates the conduction time through the A-V node since the interval between the atrial stimulus and the initial deflection of atrial activation recorded from an area adjacent to the A-V node did not vary more than 3 msec during digitalization, a change that is insignificant in comparison with the total A-V conduction time being measured.

A-V nodal refractory period: This period was determined by pacing the right atrium with a continuous train of single successive stimuli for less than 6 seconds at a fixed rate. The cycle lengths for each train were reduced by 10 msec decrements until A-V nodal Wenckebach block occurred and 1:1 A-V conduction was no longer possible. Determined in this manner, the fastest atrial driving rate that allowed 1:1 A-V conduction without manifesting Wenckebach block—that is, the shortest His-His spike interval—was defined as the measure of the A-V nodal refractory period. To minimize the frequency-dependent phenomenon of A-V nodal transmission described as "fatigue,"[18] the span of the individual pacing trains was limited to 10 to 20 cycles. The A-V nodal refractory period measured by this method is analogous to the functional refractory period of the A-V node and has been shown to correlate with the functional refractory period of the A-V node determined by the extrastimulus method coupled to atrial pacing.[19] The present method was chosen to simulate the clinical situation (that is, atrial tachycardia or flutter) during which the A-V node is continuously subjected to rapid impulses at constant time intervals rather than stimulated intermittently by isolated premature impulses. The atrial refractory period may exceed the A-V nodal refractory period at a greater than toxic dose of acetylstrophanthidin[20] but in no instance was this phenomenon observed at the dose used in this study.

Subtoxic acetylstrophanthidin dose: It is not possible to record contractility indexes and S-H time at the arrhythmogenic toxic dose since the cycle lengths were not constant. For this reason, a maximal cumulative dose of acetylstrophanthidin that the animals tolerated without manifesting toxic arrhythmias was taken as the subtoxic dose. The arrhythmogenic toxic dose is only 5 μg/kg (one dose) more than the subtoxic dose defined here and may be in a practical sense interchangeable with the latter.

Data Analysis

To normalize for differences in the toxic dose within as well as between the experimental groups, the observed values in each animal were related to the time-related cumulative dose of acetylstrophanthidin, and the values derived from the dose-response curves corresponding to 0, 25, 50, 75 and 100 percent of the subtoxic dose were subjected to statistical analysis. The dose-response data were assessed by analysis of variance (F) for simple linear regression.[21] Significance of the differences from the control values in each animal group and between the experimental groups was tested by appropriate *t* tests.

Results

Control Group (Pentobarbital)

In the three dogs anesthetized with pentobarbital and not given acetylstrophanthidin, the changes in the indexes of contractility and atrioventricular conduction over the time course (75 minutes) corresponding to the experimental studies were minimal. Thus, the maximal range of average dP/dt max and dP/dt-40 did not exceed 232 and 197 mm Hg/sec, respectively. The S-H time and A-V nodal refractory

period remained constant within the range of 5 and 3 msec, respectively. In each dog, the left ventricular end-diastolic pressure varied no more than 2 mm Hg and the left ventricular systolic pressure no more than 15 mm Hg.

Group I

In this group the animals were without autonomic blockade (morphine anesthesia with supplemental pentobarbital) (Table I). Illustrative tracings and the results obtained in one of the animals are shown in Figures 2 and 3. After the first dose of acetylstrophanthidin, dP/dt max and dP/dt-40 increased promptly and continued to increase to almost double the control value near the toxic dose. The S-H time and A-V nodal refractory period initially showed no change and then began to increase after two thirds of the subtoxic dose of acetylstrophanthidin was given.

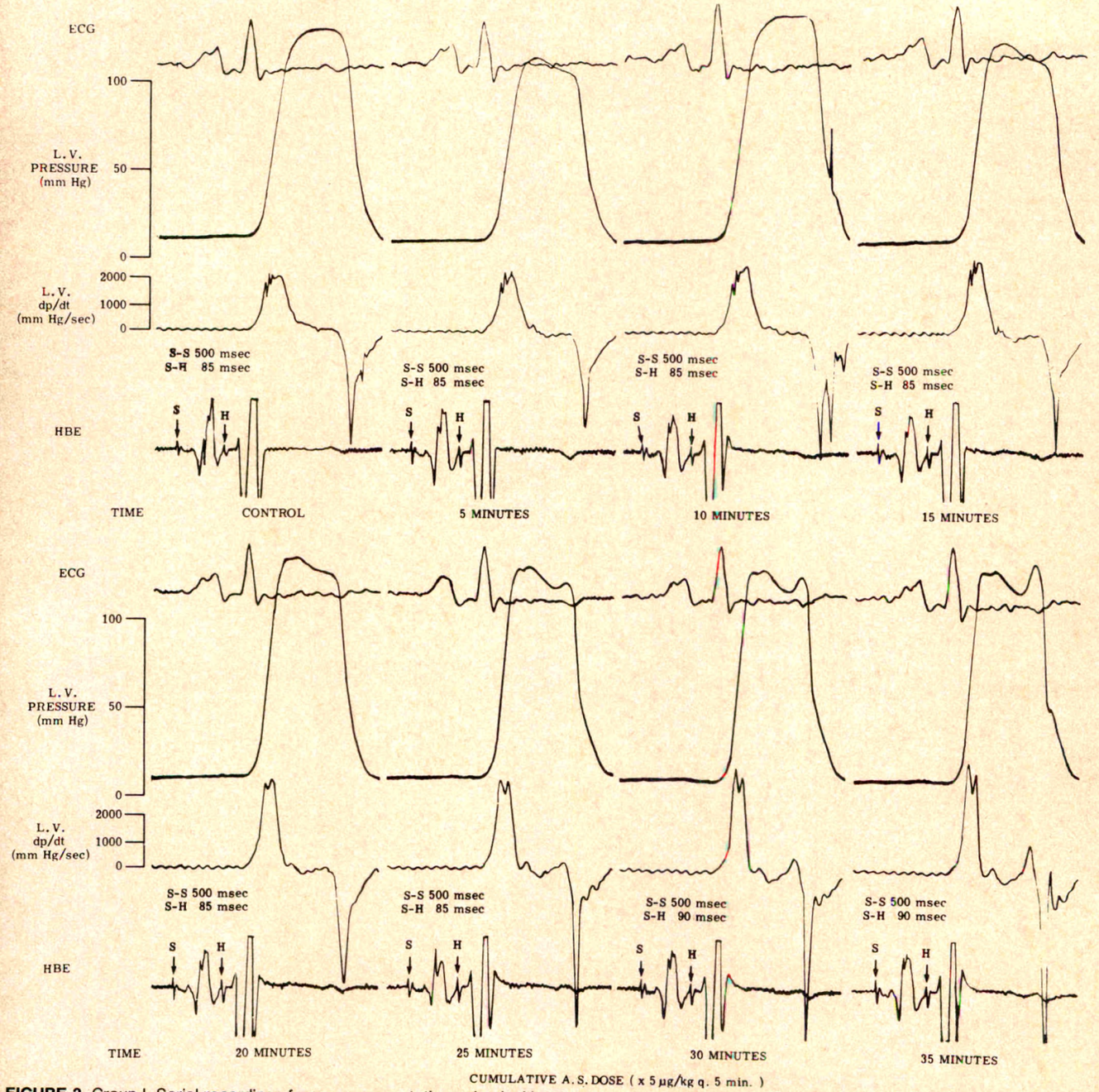

FIGURE 2. Group I. Serial recordings from a representative animal without autonomic nervous blockade during administration of acetylstrophanthidin (A. S.), 5 µg/kg every 5 minutes. Note the prompt and progressive increase in the maximal rate of rise of left ventricular pressure (dp/dt) with no change in A-V conduction time (S-H) until two thirds of the subtoxic dose of acetylstrophanthidin was given. Basic cycle length (S-S) = 500 msec; ECG = electrocardiogram; H = His bundle potential; HBE = His bundle electrogram; L.V. = left ventricular; S = atrial pacing impulse.

The potential reserve of the A-V node to delay A-V conduction was evaluated in the control state by rapid atrial pacing. S-H time measured at the shortest cycle length that allowed 1:1 A-V conduction averaged 146 ± 7 msec (mean ± standard error of the mean), which is 54 percent greater than the control value (95 ± 5 msec) at the basic cycle length of 500 msec. Since contractility indexes demonstrated comparable percentage increases in response to digitalis in this study, both contractility indexes and A-V conduction variables were included in one diagram for comparative purposes (Fig. 4).

Figure 4 shows the dose-response curves of contractile and conduction indexes expressed as percentage increases plotted against the subtoxic dose of acetylstrophanthidin in all five dogs studied. dP/dt max, dP/dt-40 and S-H time were measured at the basic cycle length of 500 msec. Progressive increases in dose of digitalis resulted in a rapid and progressive rise in the contractility indexes in all animals. Increases in dP/dt max and dP/dt-40 were linearly related to the administered dose of acetylstrophanthidin ($F = 17.08$, $P < 0.001$; $F = 10.12$, $P < 0.005$, respectively). At the subtoxic dose, acetylstrophanthidin produced an increase in dP/dt max of 63 ± 11 percent from the control value of 2,192 ± 180 mm Hg/sec and in dP/dt-40 by 50 ± 16 percent above the control value of 1,737 ± 95 mm Hg/sec.

On the other hand, the S-H time remained nearly constant at less than 75 percent of the subtoxic dose. At this dose, the average S-H time increased 6 ± 3 percent above the control value of 95 ± 5 msec to 101 ± 7 msec ($0.05 < P < 0.1$). The A-V nodal refractory period increased from the control level of 190 ± 3 msec to 212 ± 9 msec at the subtoxic dose ($F = 10.11$, $P < 0.005$). This increase in the A-V nodal refractory period was minimal in the initial phase of digitalization, and a significant increase occurred at and above 75 percent of the subtoxic dose of acetylstrophanthidin ($P < 0.01$). Both the S-H time and the A-V nodal refractory period tended to increase more rapidly just before the development of toxic arrhythmias.

During the course of digitalis administration, the left ventricular end-diastolic pressure remained either constant or decreased, and the left ventricular systolic pressure tended to increase in all animals except one. The average cumulative dose required to produce toxicity in this group was 37 μg/kg.

Group II

These animals underwent autonomic blockade (propranolol and atropine) (Table I, Fig. 5). In the control state before digitalis administration, the average dP/dt max and dP/dt-40 were lower than values in the animals with intact autonomic system (Group I) or atropinized animals (Group III) because of the myocardial depressant effect of propranolol.

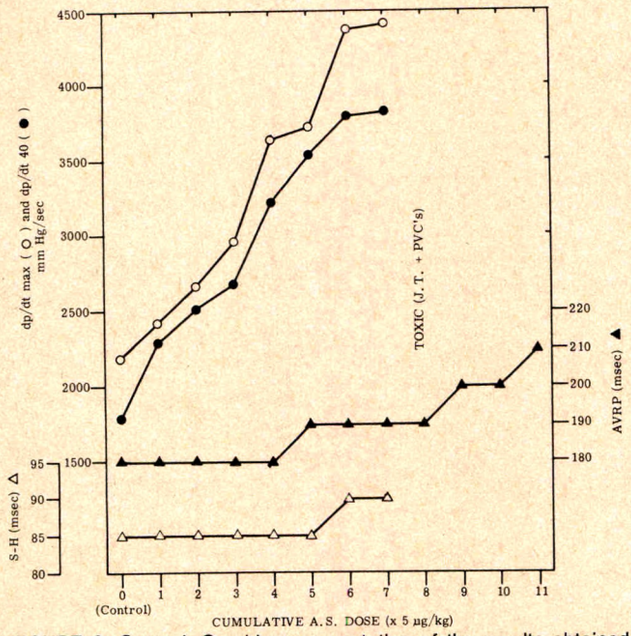

FIGURE 3. Group I. Graphic representation of the results obtained from the dog illustrated in Figure 2. Junctional tachycardia (J. T.) and multiple premature ventricular beats (PVC's) developed after the eighth dose of acetylstrophanthidin (A. S.) which is one dose (5 μg/kg) more than the subtoxic dose (seventh dose). AVRP = A-V nodal refractory period; dp/dt max = maximal rate of rise of left ventricular pressure; dp/dt-40 = dp/dt at 40 mm Hg left ventricular pressure; S-H = atrial stimulus to His potential time.

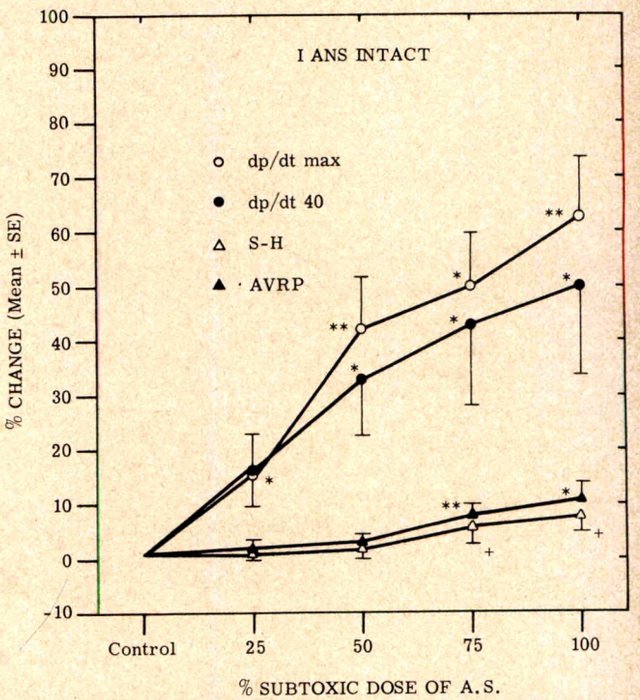

FIGURE 4. Group I. Dogs with intact autonomic nervous system (ANS) (morphine anesthesia with supplemental pentobarbital). Average percent changes ± standard error (SE) in maximal rate of rise of left ventricular pressure (dp/dt max), dp/dt at 40 mm Hg left ventricular pressure (dp/dt 40), atrioventricular conduction time (S-H) and A-V nodal refractory period (AVRP) during administration of acetylstrophanthidin (A. S.). * = $P < 0.05$, ** = $P < 0.01$, † = $P < 0.1$ compared with control values. The P values were computed in absolute units using paired t tests.

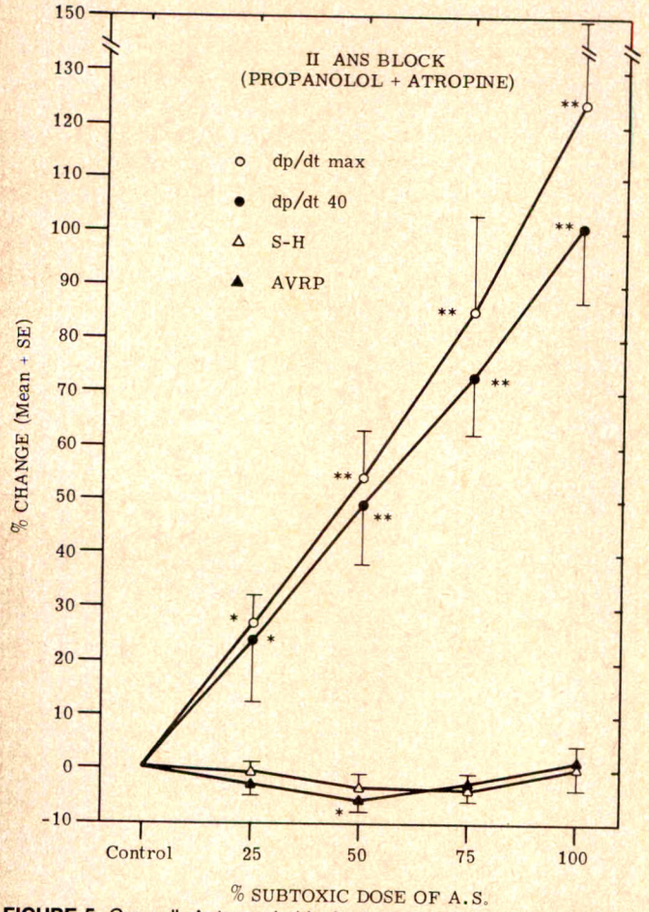

FIGURE 5. Group II. Autonomic blockade (propranolol and atropine). Conventions and abbreviations as in Figure 4. Note the initial decreases in S-H time and A-V nodal refractory period. The marked percent increases in dp/dt max and dp/dt 40 at subtoxic doses are partly attributable to control values that were lower than in other groups.

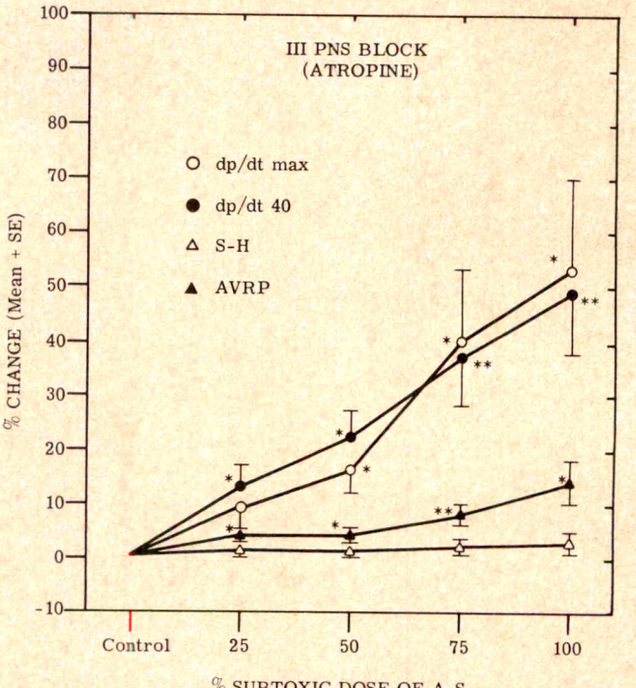

FIGURE 6. Group III. Parasympathetic (PNS) blockade (atropine). Conventions and abbreviations as in Figure 4. There is no significant change in S-H time. The A-V nodal refractory period shows an early rise with a further increase when 75 percent of the subtoxic dose of acetylstrophanthidin is given.

Digitalis administration promptly augmented contractility; a linear dose-related inotropic response was measured by dP/dt max ($F = 29.83$, $P < 0.001$) and dP/dt-40 ($F = 36.35$, $P < 0.001$). At the subtoxic dose, dP/dt max increased 124 ± 29 percent above the control value of 1,512 ± 125 mm Hg/sec and dP/dt-40 increased 101 ± 14 percent above the control value of 1,342 ± 104 mm Hg/sec. The larger percentage increases in contractility indexes, approximately twice as great as those attained by other groups, were due in part to the lower control values and in part to the larger amount of acetylstrophanthidin required to produce toxicity (average 54 μg/kg). In absolute terms, the average dP/dt max and dP/dt-40 at the subtoxic dose of acetylstrophanthidin were 3,345 ± 394 mm and 2,689 ± 247 mm Hg/sec, respectively. These values were not significantly different from those attained by the group without autonomic blockade ($P > 0.05$).

The control values for S-H time (111 ± 4 msec) and A-V nodal refractory period (254 ± 16 msec) exceeded those of the animals with intact autonomic system (Group I) or given atropine (Group III) ($P < 0.05$). This was attributed to the beta adrenergic blocking effect of propranolol on the A-V node which overrode the vagolytic effect of atropine. As digitalis administration progressed, the S-H time and A-V nodal refractory period tended to decrease until 50 percent of the subtoxic dose was given and thereafter began to increase, but not above the control values even at the subtoxic dose ($P > 0.05$). The decrease in the A-V nodal refractory period at 50 percent of the subtoxic dose was statistically significant compared with its control value ($P < 0.05$). There was a poor linear regression between the administered dose of acetylstrophanthidin and both S-H time ($F = 0.15$, P = not significant) and A-V nodal refractory period ($F = 0.01$, P , not significant).

To exclude the possibility that propranolol maximally blocked the A-V node to preclude a further response to acetylstrophanthidin, the S-H time was also measured in each dog in the control state (before administration of digitalis but after administration of propranolol and atropine) at the shortest cycle lengths that allowed 1:1 A-V conduction. The results showed that rapid atrial pacing alone prolonged S-H time to 181 ± 6 msec, a value 63 percent greater than that obtained at the basic cycle length of 500 msec.

Digitalis administration resulted in a progressive decrease in left ventricular end-diastolic pressure in four animals and no change in one animal; peak systolic pressure increased in all.

Group III

These animals had parasympathetic blockade (atropine) (Table I, Fig. 6). The average control values of dP/dt max and dP/dt-40 in the animals given atropine were greater than those of the other two experimental groups. Since the administration of atropine (0.05 mg/kg) resulted in variable responses (dP/dt max and dP/dt-40 decreased in three dogs, increased in one dog and did not change in one dog), the higher control values were not attributable to a vagolytic effect as such on myocardial contractility.

After the administration of acetylstrophanthidin, the slopes of the dose-response curves of dP/dt max and dP/dt-40 were essentially similar in absolute terms to those noted in animals with or without autonomic blockade. A significant linear regression existed between the time-related dose versus dP/dt max ($F = 10.62$, $P < 0.005$) and dP/dt-40 ($F = 26.35$, $P < 0.001$). At the subtoxic dose, dP/dt max increased by 53 ± 17 percent from a control value of 3,131 ± 363 mm Hg/sec, and dP/dt-40 by 49 ± 11 percent from a control value of 2,317 ± 132 mm Hg/sec.

The S-H time and A-V nodal refractory period in the control state were less than those values recorded in animals without autonomic blockade (Group I), but the differences did not reach statistical significance. During digitalis administration, the increase in S-H time, from 89 ± 4 msec to 92 ± 5 msec, was not statistically significant. Although changes in the A-V nodal refractory period after administration of the drug related to the cumulative dose ($F = 21.55$, $P < 0.001$), the small increase noted at 25 percent of the subtoxic dose, 4 ± 1 percent above a control value of 180 ± 3 msec ($P < 0.005$), remained unchanged until 75 percent of the subtoxic dose was administered. At and above the latter dosage, there was a rise to a maximum of 204 ± 5 msec, a 14 ± 4 percent increase above the control value.

Left ventricular systolic pressure increased and left ventricular end-diastolic pressure decreased or remained unchanged in all animals. The average cumulative dose of acetylstrophanthidin was 39 μg/kg.

Discussion

Inotropic Action of Acetylstrophanthidin

Maximal dP/dt is well established as a sensitive indicator of acute variations in the inotropic state of the intact heart, provided heart rate, preload and afterload are held constant[22] or when its measurement is interpreted with appraisal of these hemodynamic variables.[23] In this study heart rate was fixed, left ventricular end-diastolic pressure either remained constant or tended to decrease and ventricular peak systolic pressure showed a variable increase. Thus, the progressive increase in maximal dP/dt can be interpreted to indicate an enhanced inotropic state. Since the variable increase in left ventricular systolic pressure could contribute to the increase in maximal dP/dt, the first derivative of left ventricular pressure was measured at 40 mm Hg of developed left ventricular pressure, that is, dP/dt-40, to provide an additional index of contractility independent of outflow impedance.[17,22,23] In all animals, dP/dt-40 occurred at a point lower than dP/dt max on the first derivative curve and, therefore, was not conditioned by variation in mean aortic pressure or by the timing of aortic valve opening.

This study confirms that the onset of the inotropic effect of acetylstrophanthidin is rapidly manifested within a few minutes of drug administration and that there is progressive augmentation in contractility corresponding to the dose administered. Such a dose-related linear increase in myocardial contractility has been demonstrated in isolated cat papillary muscle[24]; in anesthetized animals receiving acetylstrophanthidin,[3,4] ouabain[2,4,25] and digoxin[4]; and in man given ouabain.[1] Since digitalis augments contractility more in anesthetized animals than in awake animals,[5] our results may reflect to some extent an exaggerated response. However, there is no convincing evidence in the awake dog or in man that precludes the retention of the linearly dose-related inotropic response to digitalis.

Autonomic Nervous System and Inotropic Action of Digitalis

Experimentally it can be demonstrated that digitalis activates the carotid sinus baroreceptors to reflexly withdraw sympathetic nerve traffic to the heart.[26] This decrease in sympathetic tone reduces the contractile force of the heart to counteract the enhanced inotropic state expected as a direct result of digitalis. In competition with this indirect reflex withdrawal of cardiac sympathetic stimulation, digitalis directly increases electrical activity in the cardiac sympathetic nerves.[27] If the described reflex sympathetic withdrawal[26,28] or stimulatory effect of digitalis on the sympathetic nerves were hemodynamically significant, one would expect directionally different inotropic responses depending upon the existing autonomic tone. Failure in our study and others[5] conducted in awake dogs to disclose such differential effects under various autonomic interventions suggests that the modification of the direct inotropic effect of digitalis by the autonomic nervous system, if present, must be small.

In this study, dogs with autonomic blockade showed the lowest mean contractile indexes in the control state, but acetylstrophanthidin increased contractility in these animals to values attained by the group with an intact autonomic nervous system. This finding agrees with results from studies in which total exclusion of the autonomic nervous system and beta receptor blockade[25,29,30] had no effect on the inotropic action of cardiac glycosides on the heart, thereby supporting the conclusion that the inotropic action of digitalis does not depend upon myocardial norepinephrine release.[24] Thus, in this study, the proportionate and linear increase of both dP/dt max

and dP/dt-40 in all animals with or without autonomic blockade corroborates previous data indicating that the major inotropic action of digitalis is independent of the influence of the autonomic system.

Interactions of Digitalis and Autonomic Nervous System on A-V Conduction

That digitalis exerts both a vagal and an extravagal effect on A-V conduction and refractoriness has been known since 1939 when Gold et al.[6] demonstrated that atropine attenuated but did not completely impair the ability of digitalis to slow the ventricular response to atrial fibrillation; the vagal mediation of digitalis on the A-V node has been confirmed in experimental animals.[7,11]

In this study, the A-V nodal refractory period measured in animals with an intact autonomic nervous system exceeded that measured in atropinized animals at the subtoxic dose of acetylstrophanthidin. However, the slopes of the dose-response curves of the A-V nodal refractory period to digitalis were similar in the two groups. To circumvent the possibility that a parasympathetic blocking effect of the supplemental pentobarbital might blunt a discriminatory response between animals in Group I and Group III, the experiment was also carried out under chloralose anesthesia,[31] but the results were not different and therefore not included (unpublished data). The apparent discrepancy between this study and previous investigations that demonstrated a more impressive vagal effect of digitalis on A-V nodal refractory period in the awake state[10,11] may be explained by the difference in the type and amount of digitalis used and by the fact that heightened vagal tone might characterize the awake state during the catheterization procedure. Nevertheless, the absolute increase in the average S-H time in animals with intact autonomic system was more than twice that in atropinized animals, a finding that suggests a vagally mediated digitalis effect.

The extravagal action of digitalis in slowing A-V conduction and prolonging the refractory period of the A-V node is equally well established. Thus, Mendez et al.[9] demonstrated a significant prolongation in the refractory period of the A-V node when digitalis was administered to vagotomized dogs. When the same animals were subjected not only to vagotomy but also to sympathetic denervation and adrenal ligation, thus totally eliminating the autonomic nervous system, digitalis did not prolong the refractory period until nearly lethal amounts of the drug were administered. Schaal et al.[11] confirmed that extravagal action of digitalis was an antiadrenergic effect by demonstrating no direct effect of the glycoside on A-V nodal refractoriness in awake dogs that were chronically denervated.

In our animals in Group II with pharmacologic autonomic nervous system blockade, acetylstrophanthidin failed, even in toxic doses, to increase S-H time or prolong A-V nodal refractory period. This observation, particularly apparent when comparisons are made of the dose-response curves of A-V nodal refractory period in animals in Group I (Fig. 4) and Group III (Fig. 6) as contrasted with those in Group II (Fig. 5), supports the conclusion cited, that in subtoxic doses the effect of digitalis on the A-V node is mediated almost entirely by the autonomic nervous system. The conceivable argument that digitalis could not prolong S-H time or A-V nodal refractory period beyond a maximum already resulting from the administration of propranolol to animals in Group II is untenable since each animal manifested, both in the control state and during progressive digitalization, a much longer S-H time in response to rapid atrial pacing. An interesting finding in the same group of pharmacologically denervated animals was that the S-H time and A-V nodal refractory period tended to decrease in response to digitalis until 50 percent of the subtoxic dose was given. The mechanism of this paradoxical response, which has been reported in previous studies of surgically denervated dogs,[9,11] remains unexplained.

Dissociation of Inotropic and Dromotropic Effects of Digitalis

This investigation demonstrates a temporal discrepancy between the inotropic effect of digitalis and its effect on the A-V transmission system. Specifically, contractility increases in response to small doses of digitalis; the time-related dose-response curve of contractile state is linearly correlated with the cumulative digitalis dosage and independent of autonomic influences. In contrast, digitalis effect on A-V nodal conduction and refractoriness is minimal at less than 50 percent of the toxic dose; in a subtoxic dose, the effect appears to be entirely dependent upon the interaction between digitalis and the autonomic nervous system.

Ostensibly, the differential effect of digitalis on A-V nodal conduction variables and ventricular contractility might be related to latency in A-V nodal binding of digitalis or to a lag in A-V nodal expression of digitalis effect. To test this hypothesis, a separate experiment was conducted: The A-V nodal refractory period was measured after the administration of a sufficiently large bolus injection of acetylstrophanthidin (25 μg/kg) to produce ventricular tachycardia. (It was possible in many animals to measure A-V nodal refractory period despite ventricular tachycardia employing rapid atrial pacing at even more rapid rates that still permitted 1:1 A-V conduction.) The A-V nodal refractory period promptly increased to reach a plateau within a few minutes without further increment when acetylstrophanthidin was withheld. Thus, latency is not involved in the dissociation between the dromotropic and inotropic effects of digitalis.

There is no a priori reason to anticipate a more direct correlation between the response of the ventricle and the A-V node to digitalis. First, the drug is acting on two separate anatomic structures of different cell

function. Second, as emphasized by this investigation, digitalis acts directly on the ventricular contractile mechanism but indirectly by way of the autonomic nervous system on the A-V node. Third, previous studies have indicated that the electrophysiologic effects of digitalis on the ventricle are mediated by a mechanism differing from its effect on the inotropic state of the same tissue.[2,3]

Clinical Implication

Direct application of these findings to the clinical setting requires considerable caution because of the many differences between the open chest anesthetized animal and the patient under various physiologic stresses. Nevertheless, our study does suggest several important clinical considerations. First, the optimal dose of digitalis for treating congestive heart failure may be different from that required for treatment of supraventricular tachycardias; in the former, a linear dose-related response may be expected, whereas in the latter a near toxic dose might be required for the desired A-V blocking effect, depending upon autonomic tone. Second, in the treatment of supraventricular tachycardias, the addition of cholinergic agents will enhance the blocking effect of digitalis on the A-V node.[8] However, digitalis in the absence of vagal influence may not produce further beneficial effect when added to beta receptor blocking agents. Furthermore, inadequate doses of digitalis might facilitate A-V conduction in such patients if the phenomenon shown in Figure 5 were to occur clinically. Third, the serum level of digitalis may be more useful in estimating the degree of enhanced contractile state than as a predictor of the degree of its blocking effect on the A-V node because the latter effect is predominantly determined by the level of existing autonomic tone, which varies under different physiologic stresses.

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METHODS

Improved Diagnosis in Coronary Cinearteriography with Routine Use of 110° Oblique Views and Cranial and Caudal Angulations

Comparison with Standard Transverse Oblique Views in 100 Patients

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Conventionally mounted X-ray systems for coronary cinearteriography limit angulation of the X-ray beam to the transverse plane of the patient, and use of the motorized cradle restricts rotation to 60° to 70°. These limitations of available projections seriously hamper adequate examination of the coronary arteries. With use of the Siemen's Cardoskop-U, which was designed to overcome this problem, the coronary arteries of 100 consecutive patients were examined with standard oblique projections, and in addition with cranial and caudal angulated oblique and 110° oblique projections. These arteriograms were independently examined by two expert observers. In approximately 20 percent of patients the additional views unmasked lesions that would otherwise have been missed. In a further 34 percent the diagnosis was significantly improved because the full extent of a lesion was revealed, overlap of branches was avoided or the degree of an eccentric stenosis was upgraded. In 4 of 12 patients with apparently normal arteriograms in standard projections, lesions were unmasked by the additional views.

Selective coronary cinearteriography has greatly contributed to increased accuracy in diagnosis and improved management of coronary artery disease. The enhanced contrast and resolution provided by the recently introduced cesium-iodide image intensifier have improved visualization of fine detail. Most of the X-ray systems previously available for coronary cinearteriography have used a standard mounting, with the X-ray tube below and the image intensifier above the table top, allowing projections only in the transverse plane of the patient. Use of the motorized cradle further limits the obliquity of these projections to 60° to 70°.

Like others,[1–4] we are concerned that this limitation of projections, particularly to the transverse plane of the patient, seriously hampers adequate visualization of the coronary arterial tree. In the left coronary artery the proximal portion of the left anterior descending and diagonal branches may be markedly foreshortened in the left anterior oblique projections, and the same vessels may be obscured by overlap in right anterior oblique projections. This is particularly true in a heart lying transversely within the chest or one with left ventricular enlargement. In the right coronary artery the distal vessel and the origin of posterior interventricular and acute (right) marginal branches are often also poorly demonstrated. Eccentric lesions in any region may be seriously underestimated if viewed in only one projection.

C arm systems allow cranial and caudal angulation of the X-ray beam but are awkward to use and are limited in the degree of angula-

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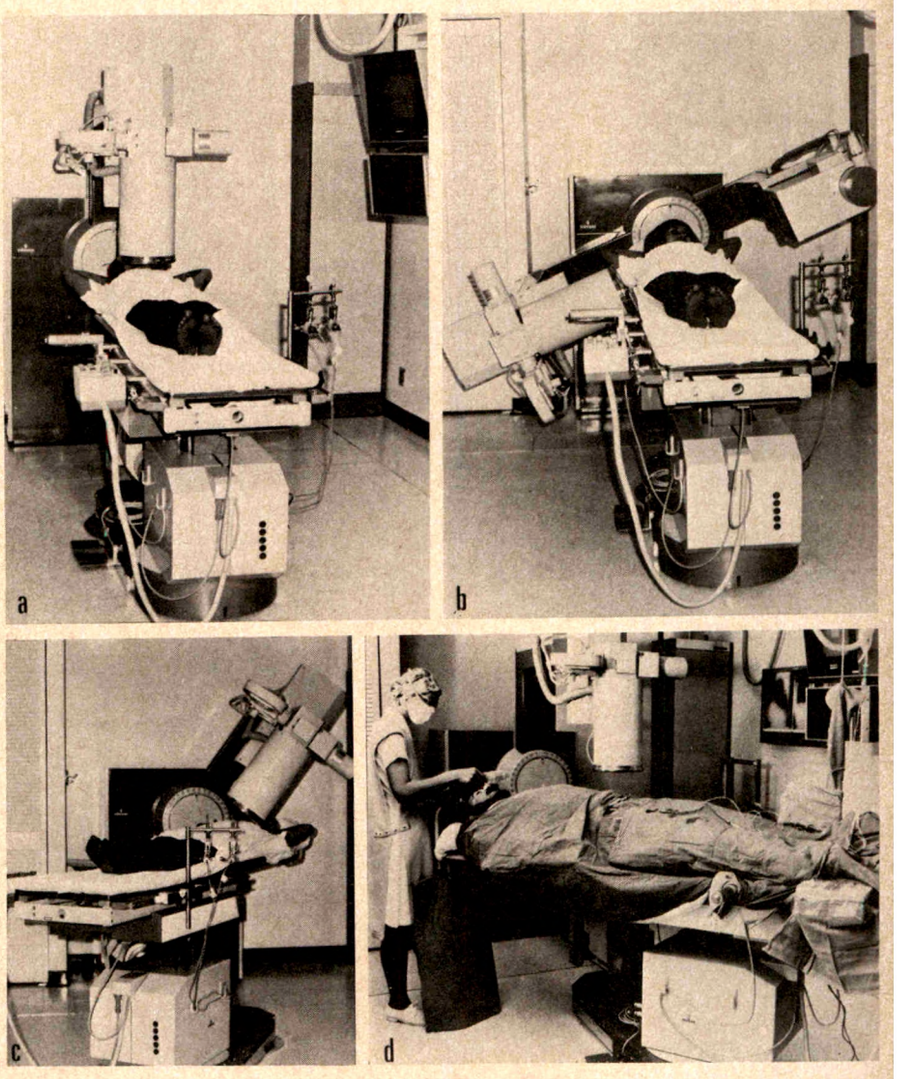

FIGURE 1. Photographs of the unit in operation. **a,** zero position of the table and image intensifier for posteroanterior fluoroscopy. The patient's arms are above the head allowing the image intensifier to be kept close to the chest wall. **b,** 110° right oblique position. The U arm has been rotated 110° to the patient's right. **c,** 50° left oblique position with a 30° clockwise turn of the table base through the isocentric cardiac axis gives a cranial projection. **d,** a 45° rotation of the patient on the table support swings the patient out from the image intensifier for physiologic studies or cardiac resuscitation.

tion. In addition, the inherent structural instability of the C arm compromises optimal use of a high resolution image intensifier mainly because of vibration during operation of the cinecamera. Because of the inadequacy of existing systems, the Siemens Cardoskop-U was designed for us to permit a multiprojectional approach to the heart. This machine combines a U arm-mounted image intensifier with a table capable of rotating horizontally about the isocentric cardiac axis and has been in clinical use at the Toronto General Hospital since June 1973. Some of our early clinical experiences with this equipment have already been reported.[2] This paper presents the results of 100 consecutive coronary cinearteriograms obtained with the Cardoskop-U, independently assessed by two experienced observers and analyzed to determine improvement of diagnosis through the use of additional (cranial, caudal and 110° oblique) projections as well as standard projections in the transverse plane.

Material and Methods

Selective coronary cinearteriograms were obtained in 100 consecutive patients with established or suspected coronary artery disease; the Judkins technique was used in 98, the Sones technique in 2. A Siemens Cardoskop-U (Fig. 1a) was used. This mounts a 7 inch high resolution image intensifier (Sirecon 17H®, Siemens) on a sturdy floor-mounted motorized U arm capable of rotating in the transverse plane of the patient about the isocentrically placed heart to 110° from the neutral (posteroanterior) position (Fig. 1b). The table turns at the base about the isocentric axis ± 100° from the neutral position (Fig. 1c). In addition, the table top may be rotated to +90° and −45° on the table support to swing the patient out from the isocentric point in case of cardiac arrest or for convenience in carrying out nonradiologic procedures (Fig. 1d).

Hand injections of 3 to 5 ml of contrast material (Renografin 76 percent®, Squibb) were used. The arteriograms were recorded on a 35 mm cine film at 30 frames/sec using an Arriflex camera. Either Agfa-Gevaert RPI or Dupont SF2 film was used and developed in a Combilabor® (Oude Delft, Netherlands) processor to a gamma level of 1.7. The frame exposure was 15 microroentgens on the image intensifier surface.

Definition of Projections

To avoid confusion between the rotational movements of the U arm and table base, these have been redefined as follows:

The movement of the U arm in the transverse plane is

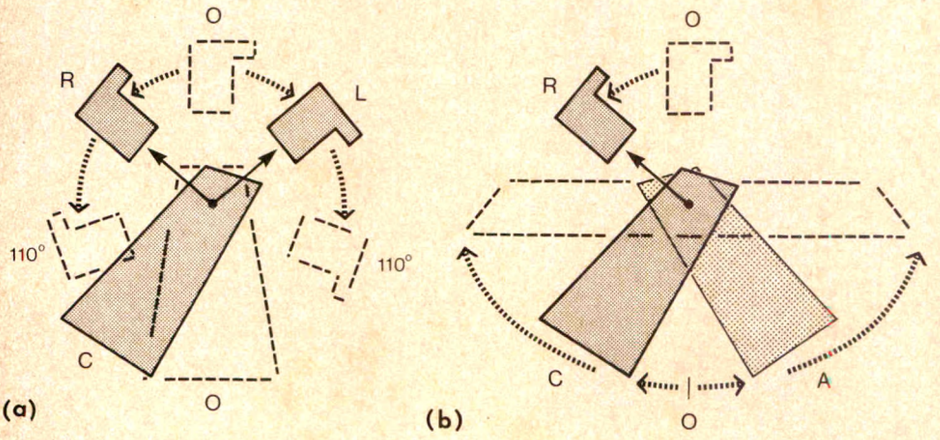

FIGURE 2. Rotational movements of U arm and table base. **a,** range of image intensifier movement to 110° right (R) or left (L) of the zero (0) position. **b,** range of rotation of table base through the isocentric cardiac axis to 100° clockwise (C) and anticlockwise (A) from the zero (0) table position. With a clockwise turn of the table base **(a),** rotation of the image intensifier to the left gives a cranial projection, and rotation to the right a caudal projection. With the image intensifier rotated to the right **(b),** a clockwise turn of the table base gives a caudal projection, and an anticlockwise turn a cranial projection. **Arrow** at the isocentric point denotes the direction of the X-ray beam.

defined by the angular position of the image intensifier to the patient's left or right of the neutral or 0° (posteroanterior) position (Fig. 2a). The terms "anterior" and "posterior" have been avoided. Thus, if the image intensifier is rotated 110° to the patient's left, this is referred to as a 110° left oblique position which, in conventional terminology, is a 70° left posterior oblique position.

The horizontal rotation of the table at its base about the isocentric cardiac point is defined as clockwise or anticlockwise (Fig. 2b). Thus, when the image intensifier is in the left oblique position a clockwise turn of the table base gives a cranial projection and an anticlockwise turn of the table base a caudal projection. When the image intensifier is in the right oblique position a clockwise turn of the table base gives a caudal projection and an anticlockwise turn a cranial projection. The projections used in the 100 patients examined are shown in Table I.

Analysis of Arteriograms

The coronary arteriograms in 100 consecutive patients were independently assessed by two experienced observers. The coronary arterial tree was subdivided anatomically as follows: (1) main left coronary artery, (2) proximal left anterior descending coronary artery, (3) diagonal branches, (4) circumflex coronary artery, (5) obtuse (left) marginal branches, (6) right coronary artery, (7) acute (right) marginal branch and (8) posterior interventricular branch.

Each of these subdivisions was analyzed in the standard views, and the effect of the additional views on this assessment recorded as follows:

1. *Normal:* when no significant abnormality was seen in any projection.
2. *Unchanged:* when assessment was not altered in the light of additional views.

TABLE I

Projections Used in 100 Coronary Arteriograms

Right Coronary Artery	Left Coronary Artery
Standard Projections	
1. 30° left oblique	1. 50°–60° left oblique
2. 50° left oblique	2. 30° right oblique
3. 60° right oblique	3. 60° right oblique
Additional Projections	
4. 110° right oblique	4. 90°–110° left oblique
5. 50° left oblique 25°–30° anticlockwise (caudal projection)	5. 50° left oblique 25°–30° clockwise (cranial projection)

See text for explanation of terms.

TABLE II

The Effect of Additional Views on Overall Assessment of 100 Coronary Arteriograms

Assessment	Observer A	Observer B
Normal	8	8
Unchanged	37	39
Improved	33	34
Unmasked	22	19
Total	100	100

See text for explanation of terms.

TABLE III

Effect of Additional Projections on Assessment of Lesions in Different Anatomic Subdivisions in 100 Coronary Arteriograms

	Assessment by Observer A			Assessment by Observer B		
Artery	Unchanged	Improved	Unmasked	Unchanged	Improved	Unmasked
Main left coronary	4	0	0	4	0	0
Proximal left anterior descending	60	30	2	58	30	2
Diagonals	29	20	12	35	20	12
Circumflex	39	6	1	39	6	1
Obtuse (left) marginal branch	44	7	1	45	6	3
Right coronary	50	4	0	51	4	0
Acute (right) marginal branch	20	6	8	23	9	7
Posterior interventricular branch	22	10	0	25	11	0

See text for explanation of terms.

3. *Improved:* when the additional views provided a better display of lesions, permitting their full length to be seen, providing freedom from overlap or permitting upgrading of the severity of a stenosis.

4. *Unmasked:* when the additional views revealed lesions not visible on the standard projections.

Results

Value of additional views: Table II shows the effect of the additional views on the overall assessment of the 100 arteriograms. Arteriograms were judged normal in eight patients. In 37 patients, as judged by

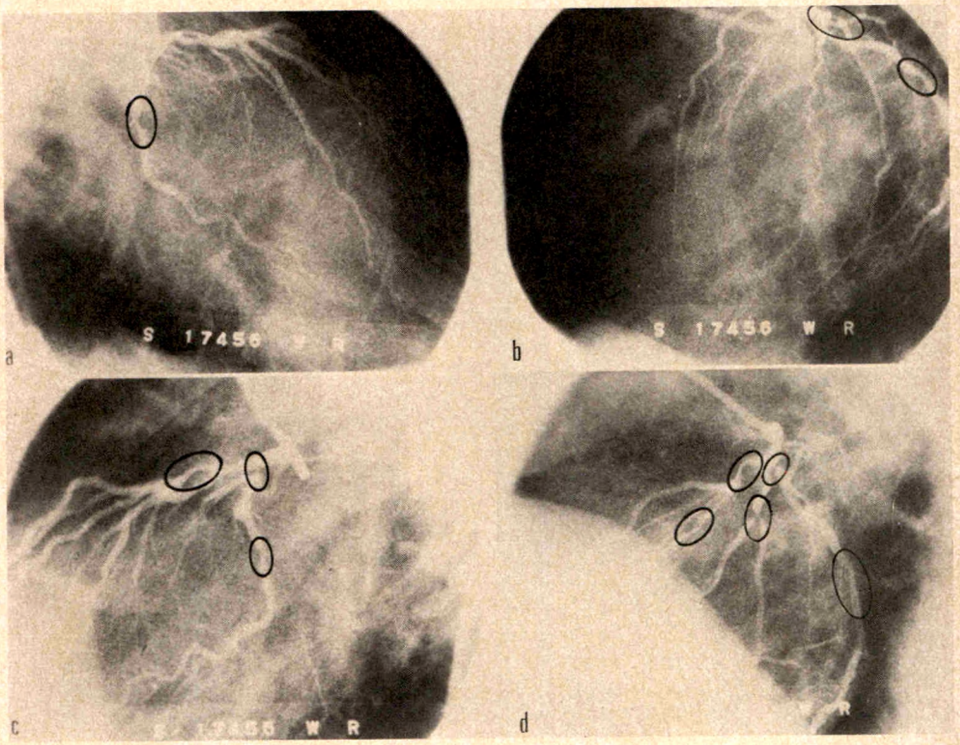

FIGURE 3. Left coronary artery. **a,** 60° right oblique view. There is a 50 percent stenosis in the mid circumflex artery. The proximal left anterior descending and first diagonal branches overlap. **b,** 50° left oblique view. The proximal left anterior descending, first diagonal, proximal circumflex and proximally arising obtuse (left) marginal vessels are overlapped and foreshortened. **c,** the 110° left oblique view with a 30° clockwise turn of the table base (cranial angulation) clearly shows a 75 percent stenosis in the proximal left anterior descending artery and unmasks a severe stenosis at the origin of the circumflex artery. **d,** 50° left oblique view with a 30° clockwise turn of the table base (cranial angulation) again shows the two severe lesions in the proximal left anterior descending and the severe lesions in the origin of the circumflex arteries. In addition, a severe stenosis at the division of a large intermediate vessel into two major branches is unmasked.

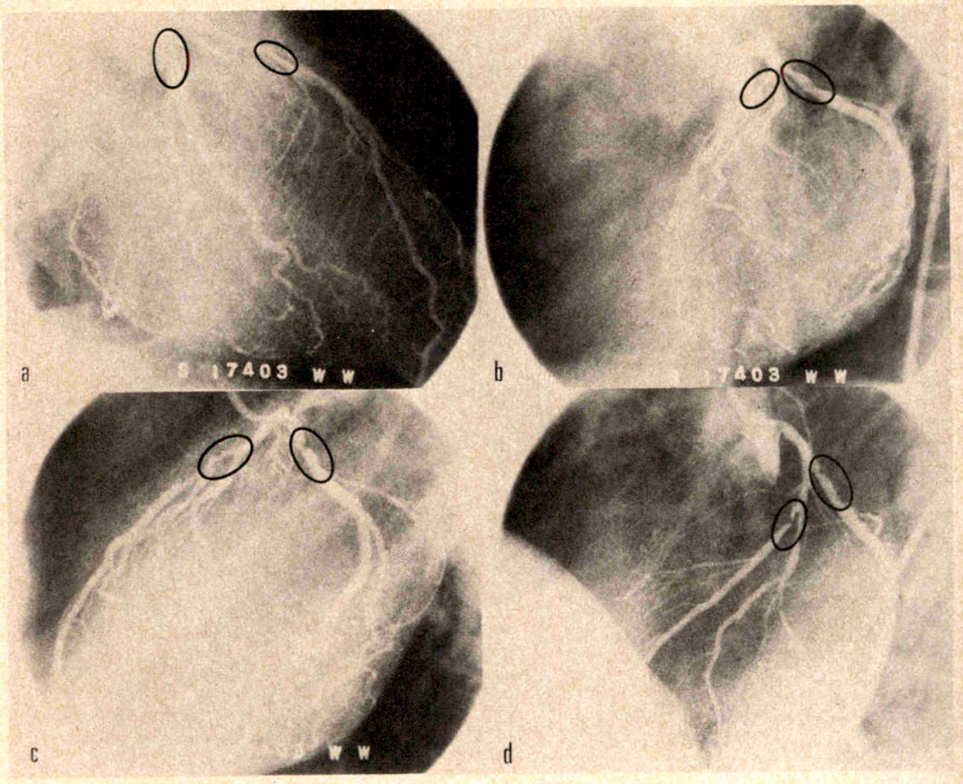

FIGURE 4. Left coronary artery. **a,** 60° right oblique view showing a 75 percent stenosis in the proximal left anterior descending artery and apparently minor lesions in the proximal circumflex artery. **b,** 50° left oblique view. The circumflex lesions appear to be more severe (50 percent stenosis) in this projection. **c,** 110° left oblique view. Both the left anterior descending and circumflex lesions appear still more severe (eccentric lesions). **d,** 50° left oblique view with a 30° clockwise turn of the table base (cranial angulation). The stenosis in the left anterior descending artery now appears to be extremely severe (90 percent).

observer A, and 39, as judged by observer B, the additional views afforded no extra diagnostic help. However, in 33 patients (observer A) and 34 patients (observer B) a more accurate display of the lesions was seen. In 22 patients (observer A) and 19 patients (observer B) the new views demonstrated lesions that were not seen in the standard transverse axial projections.

Table III shows the site of the lesions and the results of assessment by both observers. The additional views were the only ones to show lesions in diagonal branches in 12 patients (both observers) and in the acute marginal branch in 7 patients (observer B) and 8 patients (observer A). The additional views were believed to permit a more accurate assessment of the severity of the disease in all areas in some patients, and particularly in the proximal left anterior descending coronary artery (30 patients by both observers) and diagonal branches (20 patients by both observers).

Twelve patients had arteriograms considered to be normal in the standard projections; in eight the additional views also appeared normal, but in four patients lesions were unmasked (both observers). These lesions were in both the proximal anterior descending and diagonal branches in two patients, in a diagonal branch in the third and in the acute (right) marginal branch in the fourth.

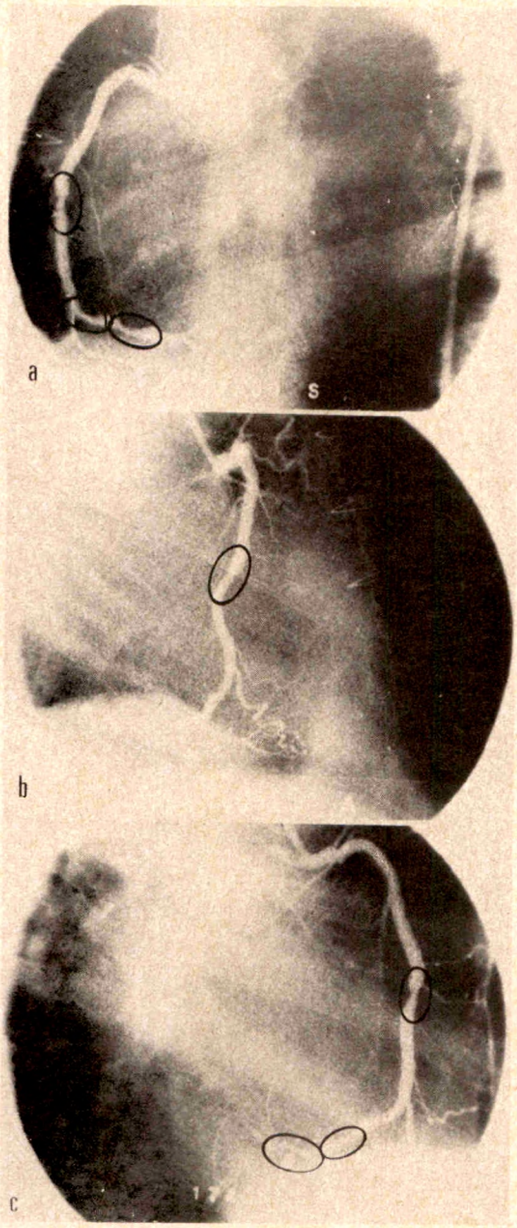

FIGURE 5. Right coronary artery. **a,** 50° left oblique view. There are 50 percent stenoses in the mid-right coronary artery and in the segment proximal to the posterior interventricular branch. **b,** 60° right oblique view. The distal right coronary arterial lesions are foreshortened and not well seen. **c,** 110° right oblique view with a 10° anticlockwise turn of the table base (cranial angulation) clears the distal right coronary artery from the diaphragm and unmasks a severe stenosis at the origin of the posterior interventricular branch.

Optimal projections for diagnosis: *Lesions in the proximal left anterior descending and diagonal branches* were seen well in a 50° left oblique view with a 25° to 30° clockwise turn of the table base (cranial projection) (Fig. 3d and 4d). The degree of left oblique rotation may have to be varied slightly to prevent overlap by the diaphragm or the spine. Occasionally a 90° or 110° left oblique view delineated lesions in the midportion of the anterior descending coronary artery more efficiently than did the standard right anterior oblique views.

The circumflex coronary artery and obtuse (left) marginal branches were seen well in either a 50° left oblique view with a 30° clockwise turn of the table base (cranial projection) (Fig. 3d and 4d) or in a 110° left oblique projection (Fig. 4c). In some patients a 110° left oblique projection still resulted in foreshortening of the proximal portion of these vessels and a 25° to 30° clockwise turn of the table base (cranial projection, Fig. 3c) had to be added to demonstrate the proximal circumflex system more clearly.

The right coronary artery, acute (right) marginal and posterior interventricular branches were demonstrated well in a 110° right oblique projection. If the diaphragm obscured the distal portion of the right coronary artery in the 110° right oblique view, then a 5° to 15° anticlockwise turn of the table base added a cranial angle sufficient to clear the diaphragm from this portion of the right coronary artery (Fig. 5c). Sometimes a 30° left oblique projection with a 25° anticlockwise turn of the table base (caudal projection) would display the distal right coronary system more efficiently, especially when the Sones technique was used and the arm board limited rotation of the U arm to about 80°.

Interobserver error: The interpretation of 20 randomly selected examinations was analyzed for interobserver error. In 19 of the 20 the overall interpretation with regard to the value of additional views (that is, "unchanged," "improved" or "unmasked") was the same for both observers. In the 20 arteriograms lesions were observed in 111 anatomic subdivisions (there were eight anatomic subdivisions per pa-

tient as previously described). Both observers agreed in their assessment in 97 of the 111 subdivisions.

Discussion

Our experience with selective coronary cinearteriography since 1960 led us to believe that the standard oblique projections obtained with conventionally mounted imaging intensification systems in use for cardiovascular examinations do not provide the most accurate diagnostic information. Our efforts commencing in 1971 to obtain an imaging system of easy maneuverability capable of providing cranial and caudal angulation resulted in the Cardoskop-U. This unit has been in clinical use in our laboratory since June 1973 and more than 1,100 patients have been studied. From this experience and from the analysis of 100 consecutive selective coronary cinearteriograms described here, we believe that routine use of cranial and caudal angulation as well as 90° and 110° oblique projections improves diagnosis in a significant number of patients.

Our work parallels and extends that of others.[1,3,4] Bunnell et al.[1] and Sos et al.[4] using serial film changers have described oblique projections with caudal and cranial angulation, respectively, for proximal left coronary branches, and L'Esperance et al.[3] have used a C arm cine system with cranial and caudal angulation in the sagittal plane. Bunnell et al.[1] attained material improvement of assessment of proximal left coronary branches in 33 of 72 coronary arteriograms.

Terminology: Previous workers have used the terms half axial,[1] lordotic[4] and sagittal angulation[3] to describe the projections used. We prefer to call these projections cranial and caudal oblique, specifying the side of the patient from which the heart is viewed and indicating the direction in which the X-ray beam is angled. We have derived our terminology from practical use of the Cardoskop-U, and it is important to realize that this terminology is unconventional in two respects: (1) The angles specified refer to the movement of components of the Cardoskop-U, not to the amount of angulation of the X-ray beam with respect to the patient. Thus the 50° left oblique view (U arm rotation) with a 30° clockwise turn of the table base (cranial angulation) in fact angles the beam 46° to the left of the patient in the transverse plane and 31° cranially in the sagittal plane. In conventional terminology this is therefore a 46° left anterior oblique view with 31° cranial angulation. (2) As already described, we have abandoned the terms anterior and posterior with respect to oblique projections in the transverse plane and use simply right or left oblique from 0° to 110°.

Advantages of unit: With the Cardoskop-U multiple projections with cranial or caudal angulation are achieved rapidly and easily with minimal disturbance of the patient. The stability of the unit allows optimal utilization of the high resolution of the image intensifier when the cine camera is operating. The 7 inch image intensifier covers an area approximately 35 percent greater than that covered by a 6 inch intensifier. By not overframing, it is possible to include the whole coronary system in the radiographic field without panning in 85 percent of patients, and complete information can usually be obtained with five projections of the left coronary artery (Table I) and three projections of the right coronary artery (50° left, 60° and 110° right oblique). If these views do not provide sufficient information, individual projections can be determined for different parts of the coronary arterial tree. This is done during fluoroscopy with adjustments of the angulation of the U arm and of the table on the basis of small test injections of contrast material.

Clinical implications: Failure to obtain more perpendicular projections of the coronary arteries may explain some of the reported discrepancies between arteriographic and postmortem findings.[5,6] It may well be necessary to redefine an adequate selective coronary arteriographic study. Apparently normal coronary arteriograms in patients with ischemic chest pain should be interpreted with caution when only standard projections are used, and studies of the natural history of coronary artery disease based on such arteriograms may be suspect.

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Comparison of Observer Performance with 16 mm Cinefluorography and 70 mm Camera Fluorography in Coronary Arteriography

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Clinical 16 mm cinefluorography and 70 mm camera fluorography were compared in 30 unselected patients undergoing coronary arteriography. Accuracy in detecting coronary arterial stenosis and collateral vessels and in assessing the degree of stenosis was similar with the two techniques. With both methods, there were significant inter- and intraobserver differences in estimating the degree of stenosis. These differences indicate that coronary arteriography is only a semiquantitative method for making decisions about treatment, prognosis and follow-up of patients. The use of more than one observer increases the likelihood that stenotic lesions will be detected. Interobserver variation in detecting collateral circulation is small.

The most commonly used recording system in coronary arteriography is cinefluorography of the output screen of image intensifiers, but camera fluorography using 70 and 105 mm film has also been used. Although the merits of the two systems have been discussed,[1–4] the techniques have not been directly compared. It is unclear whether one system is superior to the other or whether both systems are needed to obtain optimal clinical information. In this investigation we studied observer performance in assessing coronary arterial stenosis from the diagnostic information provided by 16 mm cinefluorography and 70 mm camera fluorography in coronary arteriography.

Materials and Methods

Thirty unselected patients admitted for evaluation of coronary artery disease were studied by arteriography; they were 26 men and 4 women aged 27 to 69 years.

The Judkins technique for selective coronary catheterization was used.[5] In all patients the left and the right coronary arteries were studied in the right anterior oblique and left anterior oblique projections. Additional views were obtained as deemed necessary after review of the videotape recordings. In all, there were 150 coronary cinearteriograms. In 42 instances 70 mm films of the left coronary artery were obtained in the right or left anterior oblique projections with the catheter and the patient in the same position as for the cinefluorographic recordings. In 32 instances 70 mm recordings of the right coronary artery were similarly obtained.

The same 7 inch cesium-iodide image intensifier and 0.6 mm focal spot tube were used for both the cinefluorographic and the 70 mm recordings. Exposure factors for the 16 mm cine film at 50 frames/sec were 70 to 100 kilovolts (kv) and 8 milliroentgens (mR)/frame. The 70 mm camera was operated at 4 frames/sec with exposure factors of 70 to 100 kv and 80 mR/frame. The dose of contrast medium (4 to 10 ml of Renografin®, 76 percent) was kept constant for both injections, and the rate of the manual injections was kept as constant as possible.

The 16 mm cine films and the 70 mm films of comparable injections were viewed independently and in random order without knowledge of the patients by four trained staff members who had more than 3 years' experience

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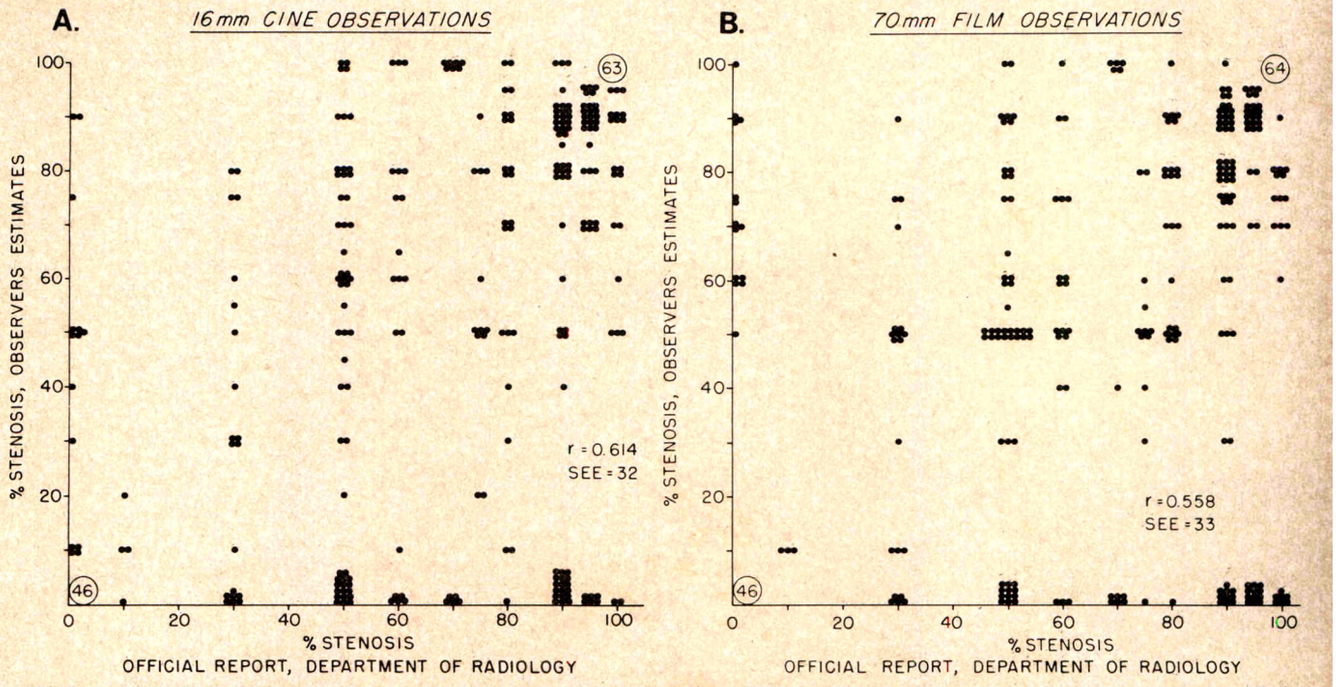

FIGURE 1. Comparison between estimates of coronary arterial stenosis in the official report and by four independent observers using 16 mm cine film **(A)** and 70 mm films **(B).** SEE = standard error of estimate. Figures in circles indicate instances of report-observer agreement on 0 percent stenosis (46) and on 100 percent stenosis (63 and 64, respectively, for the two film techniques).

in coronary angiography. They studied each recording of a coronary artery separately, assessing the location of coronary arterial stenosis and the degree of stenosis (expressed as percent reduction in luminal diameter) and collateral circulation if present. The 70 mm films were viewed first, and the 16 mm recordings 2 months later. After another 2 months, each observer again evaluated the 70 mm recordings in five patients and the 16 mm recording in five patients. In addition, one observer used a magnifying measuring device to measure 29 stenoses in the coronary arteries as seen in the 70 mm films. The measurements were made with an accuracy of 0.1 mm.

The official report on the patients from the Department of Radiology was used as a measure of the "true" presence and degree of stenosis. This report is a product of a careful simultaneous evaluation of the films by three or four observers, including both radiologists and cardiologists with 3 to 16 years' experience in coronary arteriography. It can be considered an independent panel decision and its estimates are probably closer to the truth than those of the individual observers, although it is still dependent upon the variable under study.

Results

Coronary Stenosis

Detectability: There was generally little difference between the observers' ability to detect stenoses when using the 16 mm cine film and the 70 mm films. In three instances, a stenosis was seen by all observers in the 16 mm cine film and by only one observer in the 70 mm films. In four instances the reverse was found.

Interobserver variation in grading: The four observers' estimates based on the two recording systems contained an equal number of deviations of more than 20 percent stenosis. Figure 1 shows the individual observers' estimates based on 16 mm cine film and 70 mm films, plotted against the estimates in the official report. Both plots show a similar marked scatter among observations. When only coronary arterial stenosis of more than 50 percent in luminal diameter was considered clinically significant, the number of false positive and false negative findings was very similar with both 16 mm cine film and 70 mm films (Fig. 1).

When the 29 measurements of stenoses based on 70 mm films were plotted against the observer estimates based on 16 mm cine film and 70 mm films (Fig. 2), a wide scatter among observations and no difference between the two recording methods were found. When instances in which the observers completely overlooked a stenosis are omitted, agreement between the observer estimates and the measurements was better, particularly for the 70 mm films, and similar to the agreement between observers' estimates and those of the official report (Fig. 3).

Stenosis in the left main coronary artery was reported only three times. In two cases the observers' estimates of the degree of stenosis in this artery differed by less than 20 percent. In the third case the estimates ranged from 0 to 50 percent stenosis.

When observers estimated stenoses in the right coronary artery and the left anterior descending and left circumflex branches, there was complete agreement among all four observers in 85 instances (37 percent). In 52 instances (23 percent), estimations of

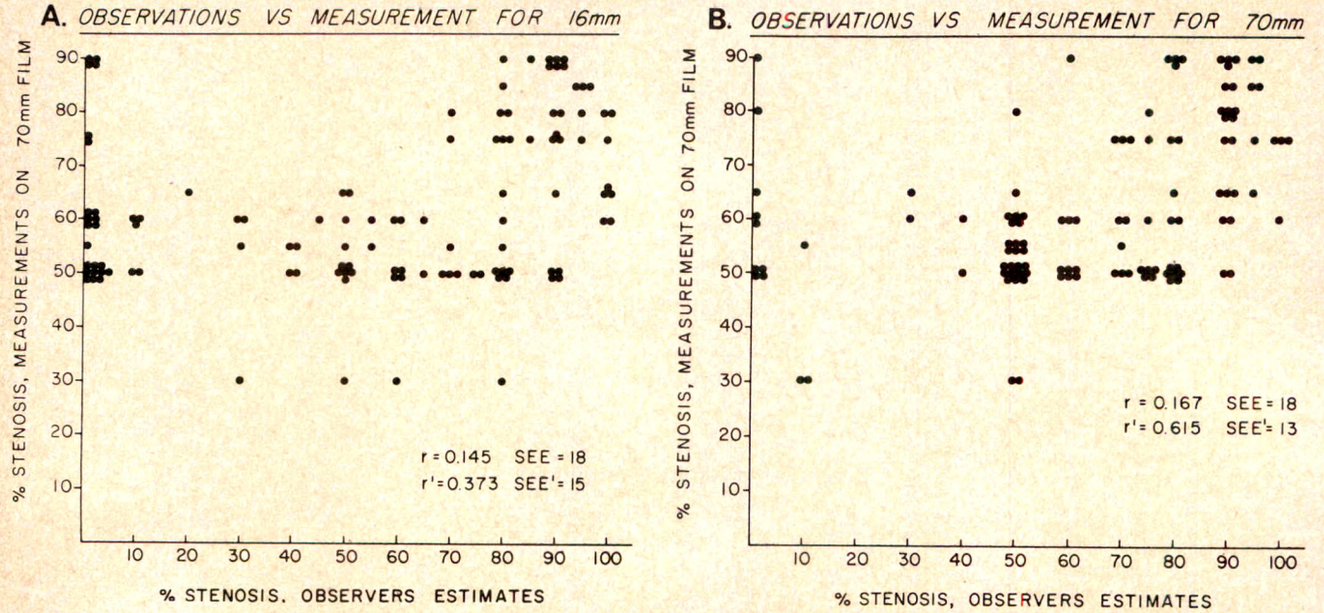

FIGURE 2. Comparison between measurements of coronary arterial stenosis on 70 mm films and four observers' estimates of stenosis based on 16 mm cine film **(A)** and 70 mm films **(B).** SEE = standard error of estimate. Instances when the observers completely missed a stenosis are not calculated in the values for r′ and SEE′.

the degree of stenosis differed by less than 20 percent; in 60 observations (26 percent), they differed by 20 to 80 percent; *and* in 31 cases (14 percent), they differed by more than 80 percent. In 40 percent of all observations of all arteries, the observers' estimates of the degree of stenosis differed by more than 20 percent. The widest variation among estimates was found with stenoses in the left anterior descending branch.

Among the 85 instances in which agreement among the observers was complete, in 20 cases the patient was judged to have normal coronary arteries and in 23 to have total occlusion of one artery. When these 43 observations are subtracted, 185 instances with various degrees of coronary arterial stenosis remain. In 49 percent of these instances there was an interobserver variation of more than 20 percent stenosis.

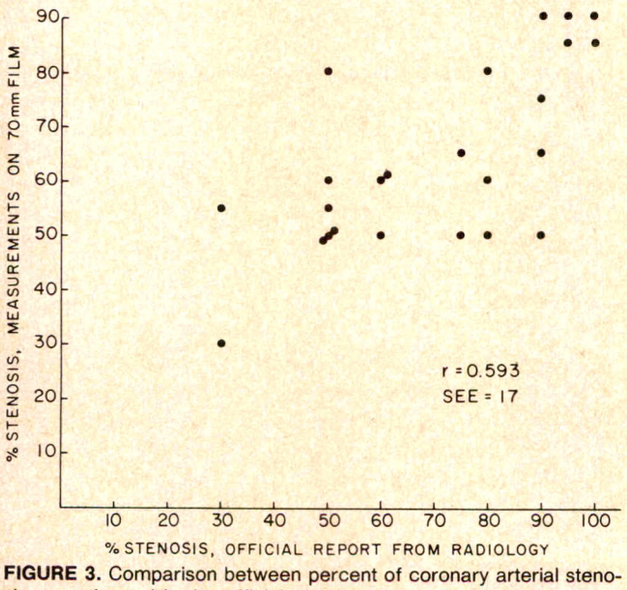

FIGURE 3. Comparison between percent of coronary arterial stenosis as estimated in the official report and as measured on 70 mm films. SEE = standard error of estimate.

Among the four observers, no two agreed on a definitely erroneous interpretation of the coronary arteriograms. In other words, stenosis would always have been detected if two observers had viewed the films. Errors in observers' estimates ranged from over- to underestimation, with no particular pattern. Two of the four observers tended to overestimate slightly the degree of stenosis. Observer performance improved only little with greater experience. When stenosis was reported, there was almost complete observer agreement on its location. Even when more than one projection was considered, the estimates of no individual observer produced as good correlation with the measurements as did the official report.

Intraobserver variation in grading: Figure 4 shows the intraobserver differences in determining the degree of stenosis from 16 mm cine recordings and 70 mm films. With the 16 mm recordings, complete agreement between the first and the second observations was seen in 36 to 48 percent of cases. Reasonable agreement between the two observations was seen in 72 to 76 percent with all four observers if variations of less than 20 percent stenosis were considered insignificant with regard to patient management.

With the 70 mm films, complete agreement between the first and the second observation was present in 60 to 80 percent of the instances. Reasonably good agreement between the two observations

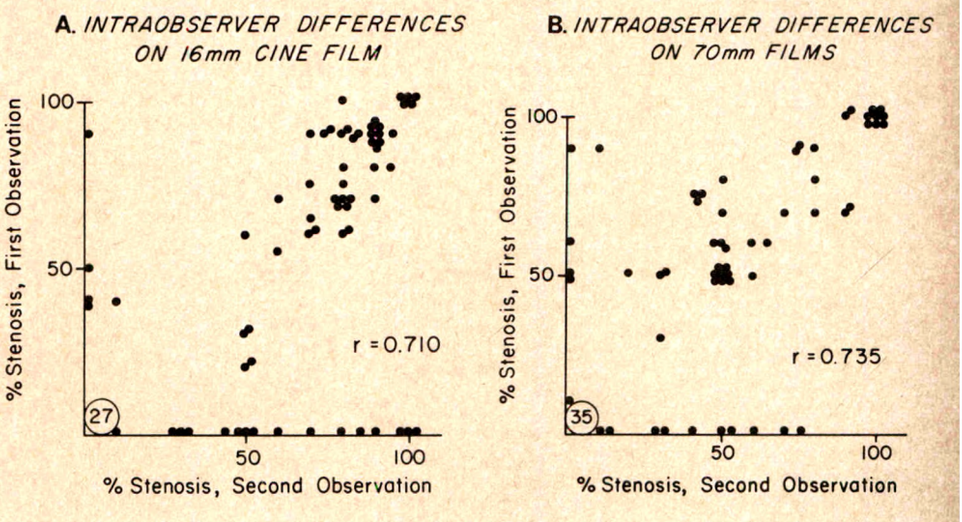

FIGURE 4. Intraobserver differences in separate observations of 16 mm cine film **(A)** and 70 mm films **(B)**. Each of the four observers reviewed the films twice with a 2 month interval between readings.

was seen in 72 to 92 percent of the observations (with less than 20 percent difference in estimation discounted). With both 16 mm film and the 70 mm films, the observer reversed his decision of more than or less than 50 percent stenosis in 18 percent of the cases.

Collateral Vessels

Collateral vessels were reported 31 times. Surprisingly, there was nearly complete agreement among the observers regarding their presence and location. In only 2 of the 31 instances did one observer not report a collateral vessel seen by the others. In five instances the collateral vessels were obviously better delineated in the 16 mm cine film than in the 70 mm films, but in four instances the reverse was true.

Discussion

This study showed no significant difference between 16 mm cine film and 70 mm camera fluorography at 4 frames/sec in depicting the degree of coronary arterial stenosis, probably because both systems provide so much information that the diagnostic process involves filtration and subtraction to extract the clinically useful data. Similar results have been obtained with the comparison of cine recordings and full size film-changer recordings in pediatric angiocardiography.[6] The intraobserver differences were somewhat less with the 70 mm than with the cine film but not significantly so. The observers agreed that information was retrieved more easily and quickly from the cine film than from the 70 mm films, possibly because the observers had considerable experience in viewing coronary cinearteriograms but only limited experience with 70 mm films.

A limitation of this study is that there is no method for determining the true degree of stenosis in the coronary arteries. Measurements of coronary arteries have been attempted, but theoretical considerations and practical experiments have shown that even with the best imaging systems available, such measurements based on 70 mm films are unreliable (particularly with arteries less than 3 mm in diameter).[7] All arteries measured in this investigation were less than 3 mm. In a recent report,[8] significant discrepancy between measurements of stenosis at coronary arteriography and at postmortem examination was found in 9 of 23 cases. The significance of these observations remains unclear. It is doubtful that routine measurement of coronary arterial stenosis would significantly alter decisions on patient care.

In contrast to our findings, it has previously been believed that cine recordings would provide better delineation of collateral vessels than other recording systems.[3] The cine technique is probably better than the serialographic film-changer method, in which the number of exposures and the length of the run are limited by various factors. Neither cine recordings nor 70 mm recordings are limited significantly by these factors.

Agreement among the observers in detecting coronary collateral flow with both systems was very good. This finding is in contrast to the considerable inter- and intraobserver differences in detecting and assessing the degree of coronary arterial stenosis. It appears that the subjective element in the detection and grading of coronary arterial stenosis is one of the major limiting factors of arteriography. On several occasions coronary arteries reported to be normal by one observer were considered totally occluded by another. On the other hand, the best agreement among the observers was seen with either normal coronary arteries or total occlusion of a coronary artery. These extremes are obviously the easiest to diagnose correctly.

Clinical implications: This study confirmed that a single observer's estimates of coronary arterial stenosis are frequently erroneous and that accuracy increases if grading is performed by more than one observer.[9] The latter is the usual situation in assessing coronary arterial stenosis in clinical practice. The diagnosis is determined not only by the viewing of a single projection of one coronary artery but also by

the combining of information from several injections into the same artery and into other coronary arteries, as well as from the left ventricular angiocardiogram and clinical information on the patient.

In this study coronary arteriography proved to be only a semiquantitative method for assessing the degree of coronary arterial stenosis. This concept is important to bear in mind when making decisions on treatment, prognosis and follow-up of patients. At present, there is no obvious way to increase the accuracy of coronary angiography. Measurements are of no value in medium-sized and smaller arteries, and there appear to be no prospects for technical improvements in the near future. Other methods are currently being evaluated (such as densitometric measurements of coronary arterial blood flow[10] or isotope studies[11]) to determine the significance of coronary arterial stenosis seen in the arteriograms.

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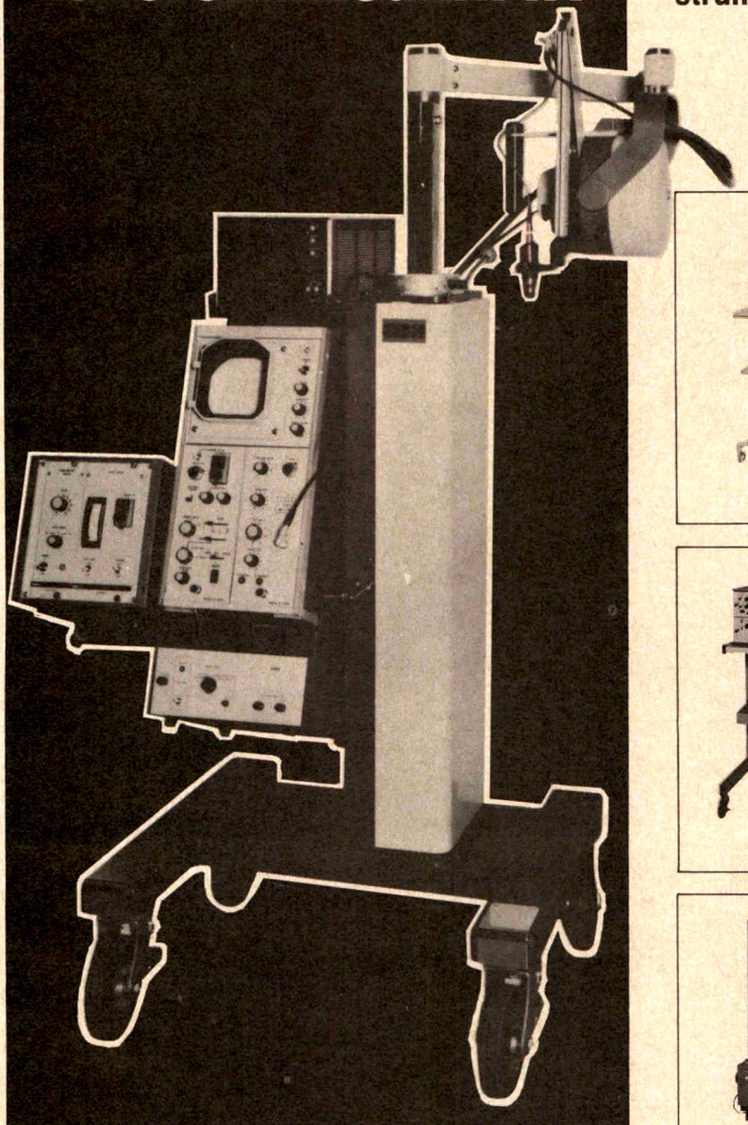

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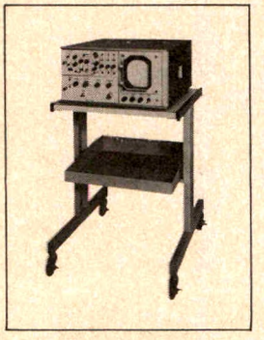

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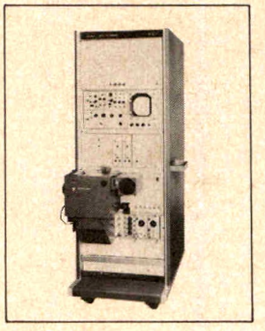

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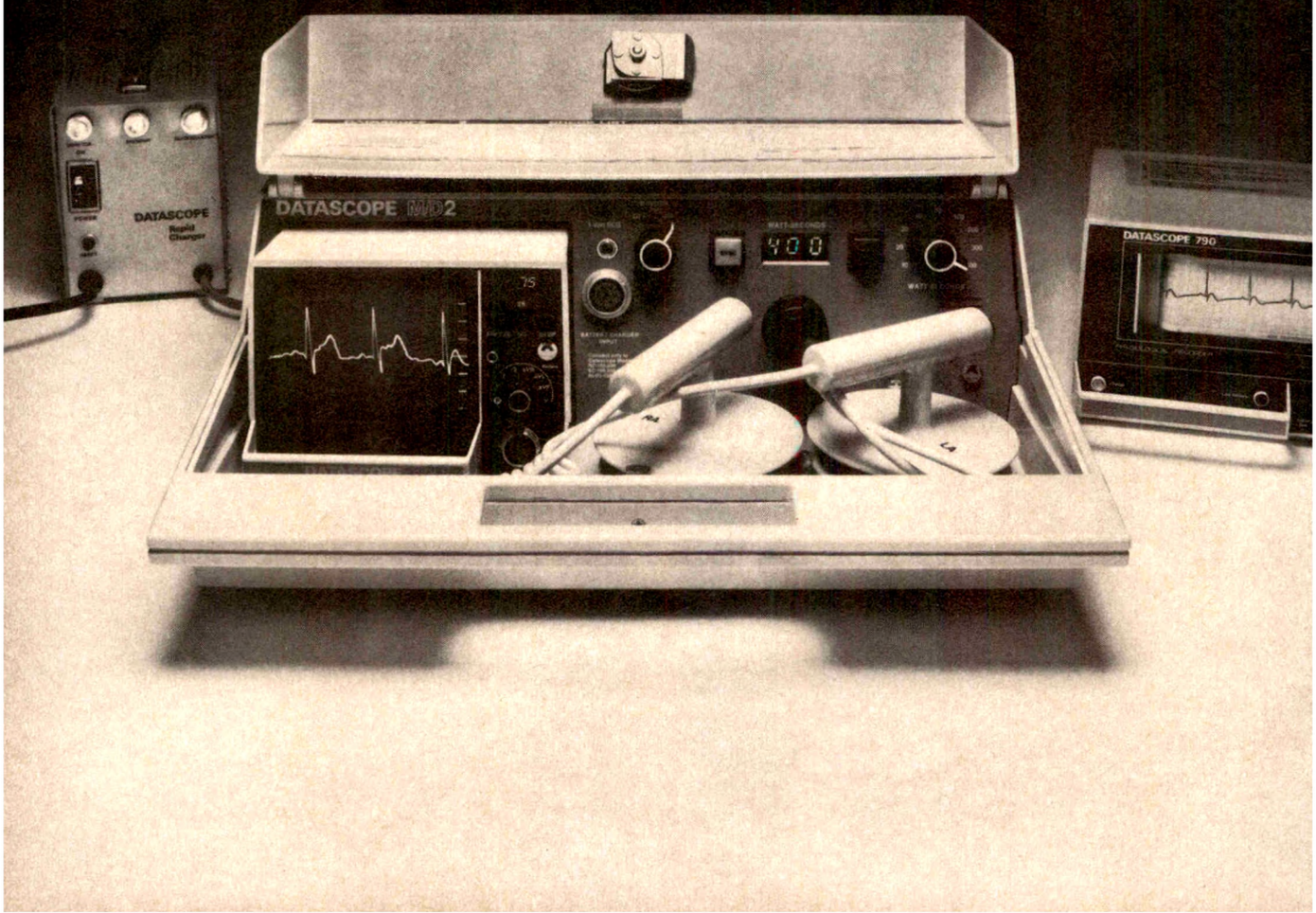

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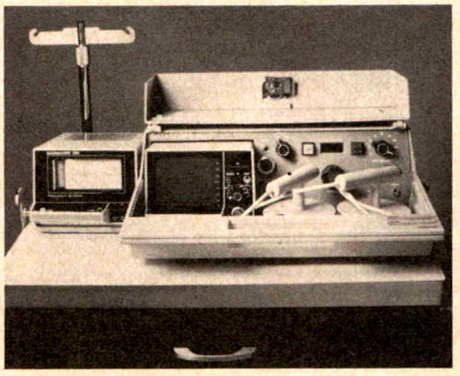

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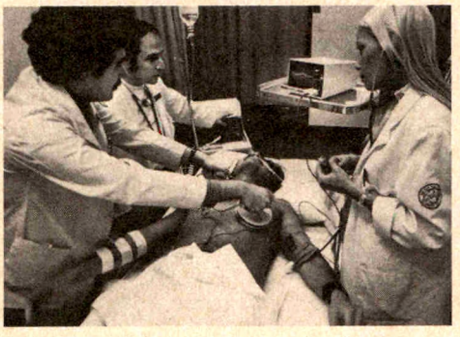

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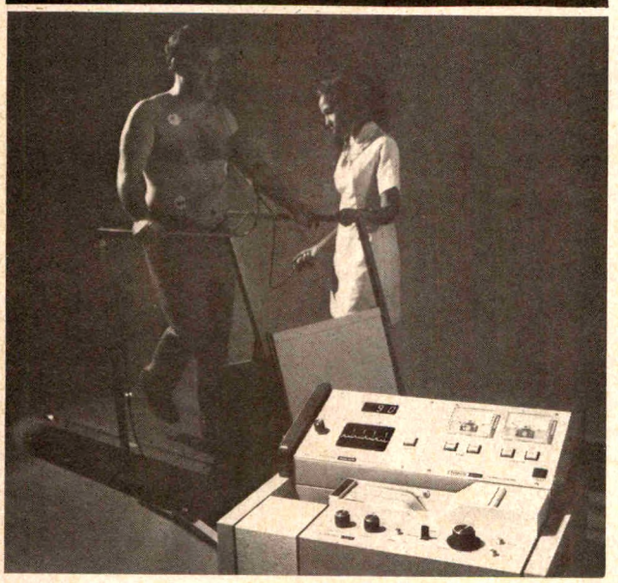

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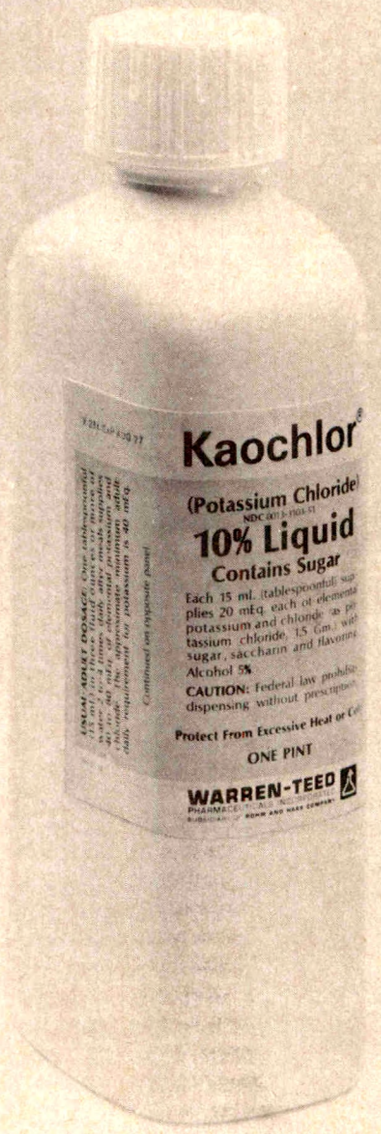

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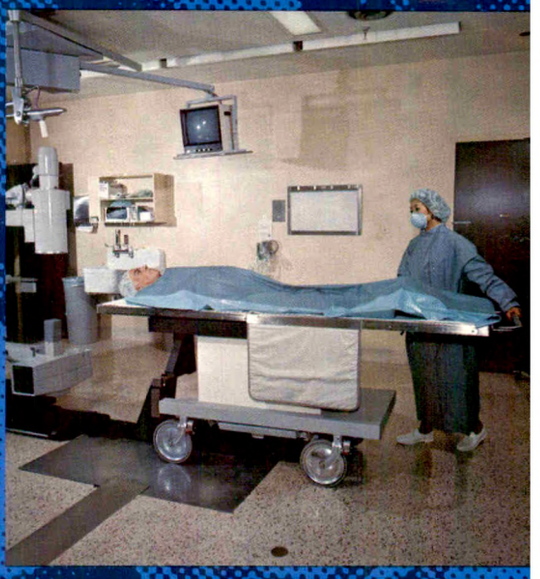

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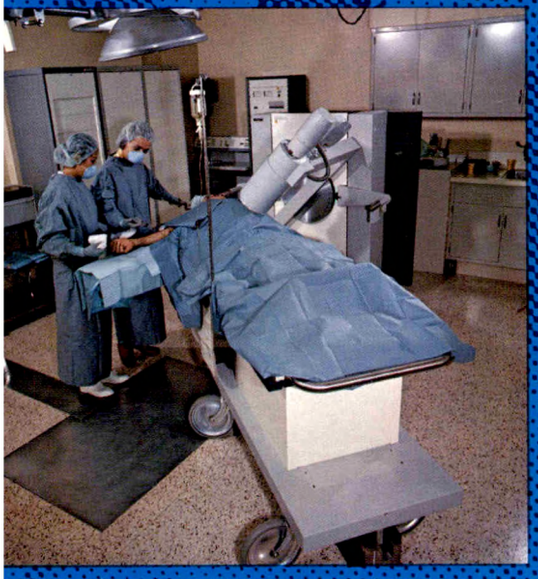

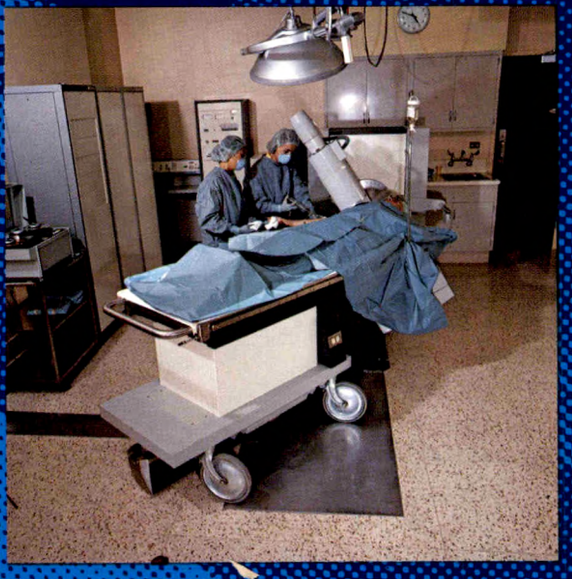

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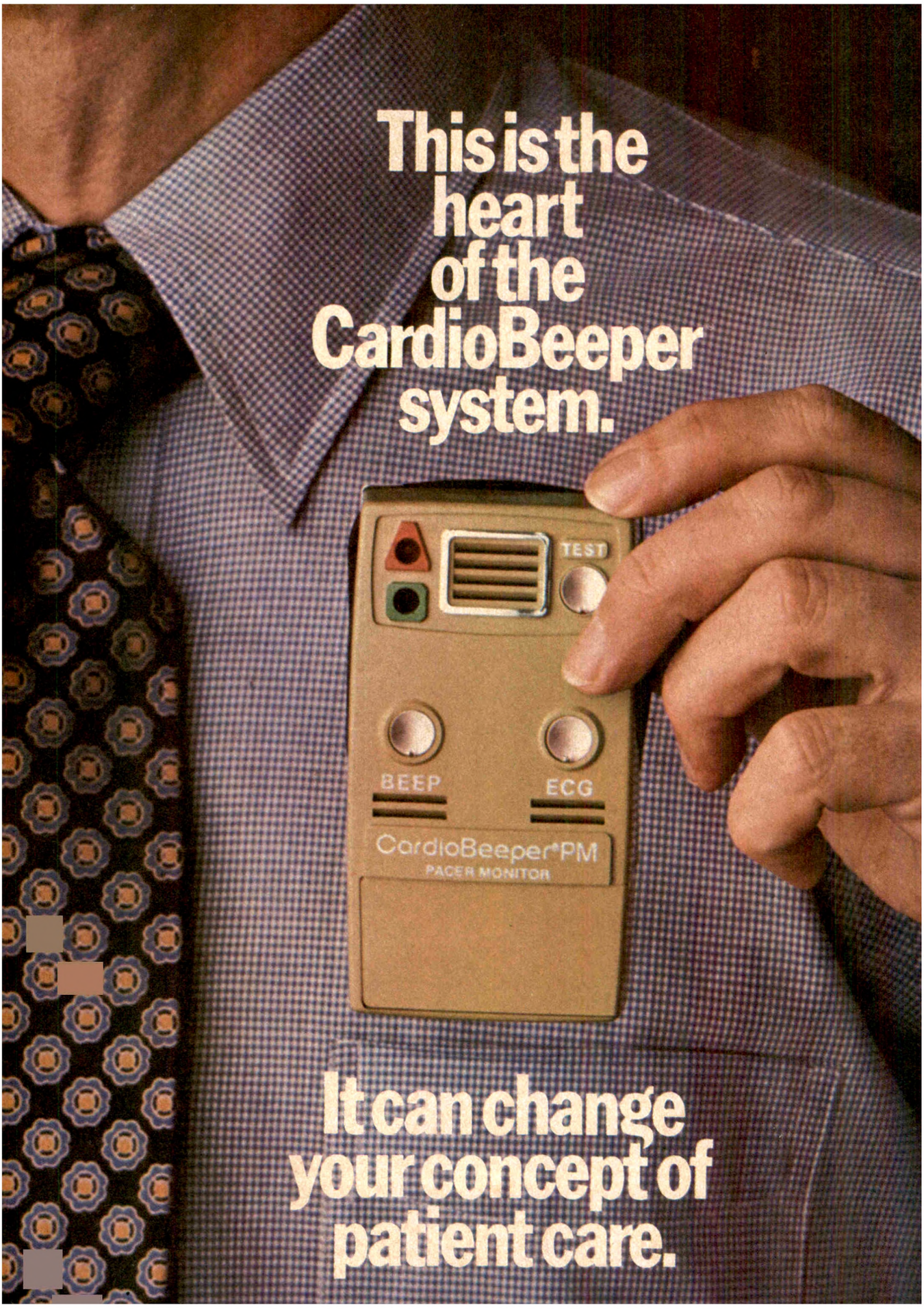
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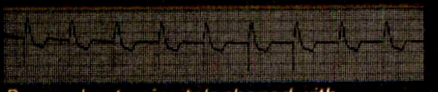

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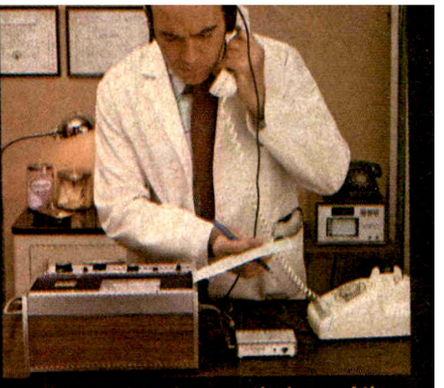

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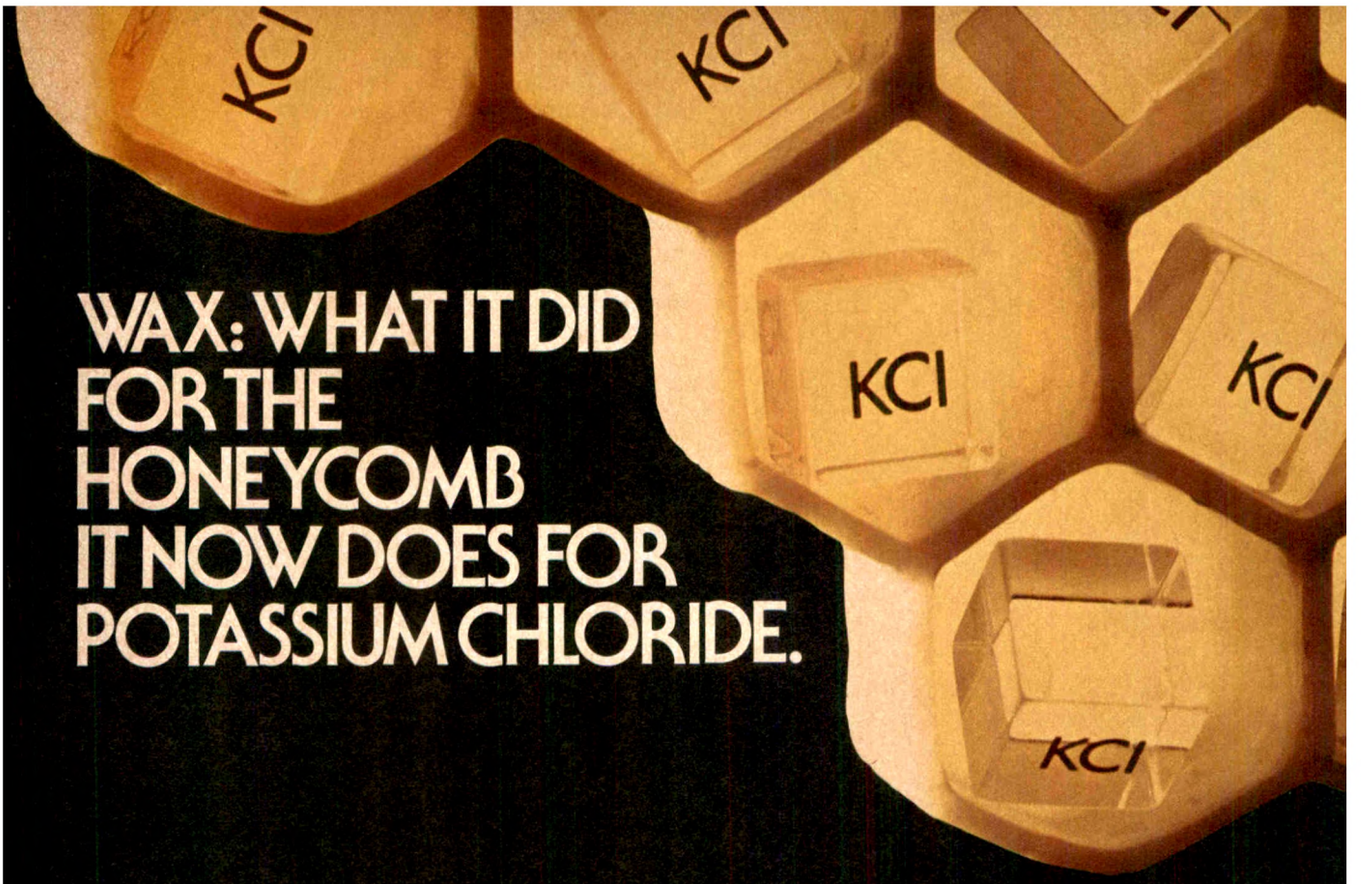

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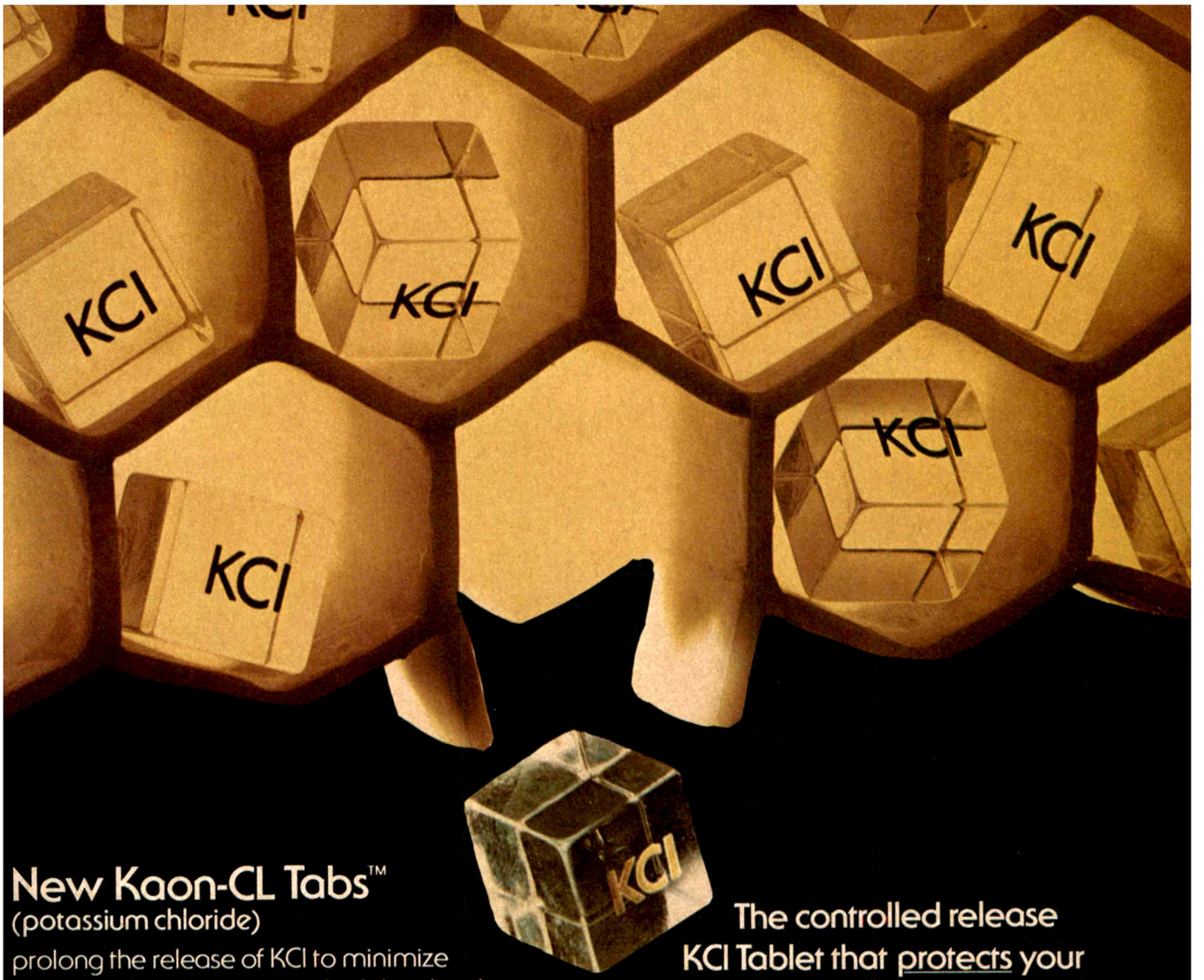
NEW KAON-CL TABS™

(potassium chloride)

CONTROLLED RELEASE TABLETS

– Potassium chloride imbedded in a wax matrix to provide controlled release, thus minimizing possible high local concentration of potassium ion near the bowel wall. The newest idea in potassium chloride supplements is as old as the beehive. Wax... provides an effective vehicle to imbed KCl



New Kaon-CL Tabs™
(potassium chloride)

prolong the release of KCl to minimize the likelihood of producing high localized concentrations of potassium within the G.I. tract...

protect your patient from the risk of hypokalemia or digitalis intoxication due to potassium depletion that diet alone cannot correct...

promote adherence to medication schedule by relieving the patient of the inconvenience of liquids...

Three-way convenience for your patients on KCl Supplements...

- because there's no palatability problem
- because there's no dilution problem
- because tablets are physically easier to carry—and to take—than liquids... an especially welcome advantage away from home—encouraging adherence to the prescribed regimen

The controlled release KCl Tablet that protects your patients on diuretics or digitalis

- against hypokalemia due to potassium depletion that cannot be adequately replaced by diet alone
- against the inconvenience of—and often confusion over—dilution of liquid supplements
- from taste-fatigue associated with liquids

Dosage: Prophylactic: 20 mEq. daily (1 tab T.I.D.)
Therapeutic: 40-100 mEq. daily
See following page for brief summary.

WARREN-TEED
PHARMACEUTICALS INCORPORATED
SUBSIDIARY OF ROHM AND HAAS COMPANY
COLUMBUS, OHIO 43215

Warren-Teed®

KAON-CL TABS™

(Potassium Chloride)

CONTROLLED RELEASE TABLETS

Description: Kaon-CL Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg. potassium chloride (equivalent to 6.67 mEq. potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: Kaon-CL Tabs is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. Kaon-CL Tabs is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

Warnings: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-CL Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric coated potassium chloride tablets (40-50 per 100,000 patient-years), a few cases associated with wax-matrix tablets have been reported. These data are from foreign marketing experience. Kaon-CL Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia, in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Dosage and Administration: Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq. per day for the prevention of hypokalemia to 40-100 mEq. per day or more for the treatment of potassium depletion.

One Kaon-CL Tabs three times daily provides 20 mEq. of potassium chloride. Two Kaon-CL Tabs three times daily provides 40 mEq. of potassium chloride.

Caution: Federal law prohibits dispensing without prescription.

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Nitrol® Nitroglycerin Ointment 2%

1955 "Because of the ineffectiveness of the conventional measures, it was suggested that a 2% nitroglycerin ointment [Nitrol] be applied to the skin....It is the authors' impression that there has been definite benefit from this therapy, when used together with all other measures for the treatment of angina pectoris....The principle of slower absorption with resulting prolonged action of an effective coronary vasodilator would seem to deserve further trial in this condition."[1]

1974 "...nitroglycerin ointment [Nitrol] exhibited a consistently prolonged beneficial influence that, in practice, has never been demonstrated for any other nitrate used in the therapy of angina."[2]

Composition: Nitroglycerin 2% in lanolin-petrolatum base. **Administration:** F to 2 inches applied to desired skin area by means of Appliruler supplied. Ad individual need, starting in lower range. **Side effects:** Headache indicates o Dizziness on standing may be the result of postural hypotension. **Contraindi** Marked anemia, increased intraocular pressure or increased intracranial pr **Supplied:** 1-oz. or 2-oz. tubes. **Caution:** Federal law prohibits dispensing wit prescription.

References: 1. Davis, J. A., and Wiesel, B. H.: Am. J. Med. Sci. **230**:259-263 (1955. **2.** Reichek, N.; Goldstein, R. E.; Redwood, D. R., and Epstein, S. E.: Circ **50**:348-352 (August) 1974.

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see next page

TWO OF THE HIGH-TECHNOLOGY SIEMENS-ELEMA PACEMAKERS NOW AVAILABLE IN AMERICA

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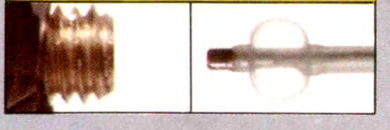

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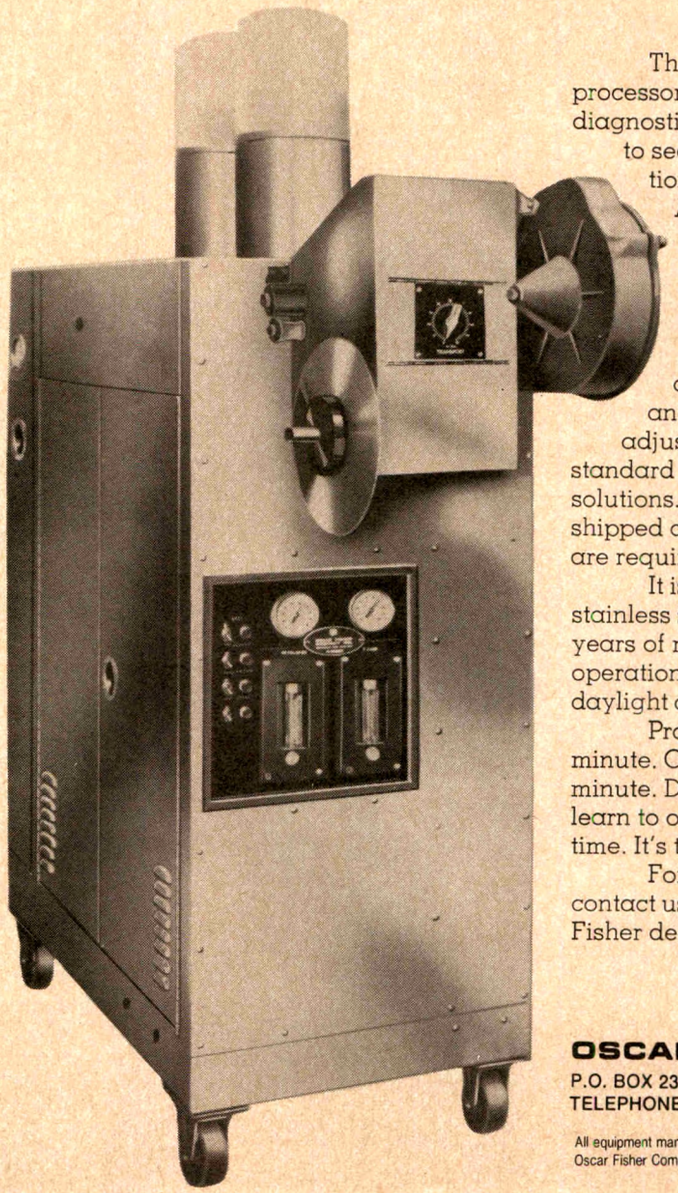

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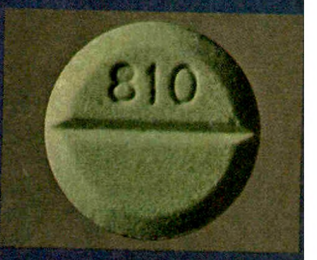

Offers all the benefits you've come to expect of sublingual ISDN:

- ☐ acts just as fast for therapeutic use...within 2 minutes
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Offers these unique advantages over the sublingual form:

Natural chewing action stimulates saliva secretion...

- ☐ helps dissolve medication more easily
- ☐ helps distribute nitrate over a larger mucosal area
- ☐ helps avoid "dry-mouth" problems

SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

* **Indications:** Based on a review of this drug by The National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack: Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily; CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE.

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS
Division of ICI United States Inc.
Wilmington, Delaware 19897

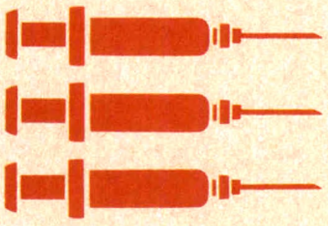
Effectiveness..

I.V. Administration Guidelines for Premature Ventricular Contractions and Tachycardia

1. Preparation of drug: Dilute before I.V. use.
2. Usual dosage range: 200-1000 mg.
3. Infusion rate: Not to exceed 25-50 mg. per minute. Total I.V. dose not to exceed 1000 mg.
4. Precautionary measures:
   a. Keep patient in supine position.
   b. Monitor electrocardiographically and discontinue if myocardial toxicity is evidenced.
   c. Measure blood pressure almost continuously and temporarily discontinue infusion if blood pressure falls more than 15 mm. Hg.

When therapeutic blood levels are required quickly, I.V. Injections

100 mg. every 5 minutes until arrhythmia suppressed (up to a maximum dose of 1 gram).



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I.V. Infusion

2-6 mg. per minute[1].
(42.8 μg./min./kg.)[2]

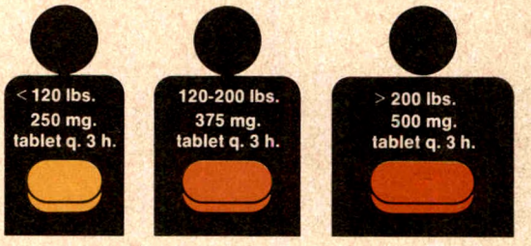
1. Wyman MG, Hammersmith L: Am J Cardiol 33:661-667, 1974
2. Bigger JT, Jr., Giardina EV: MCV Quart 9 (1): 65-76, 1973

Terminate I.V. infusion *4 hours before* oral regimen begun.

Oral Administration Guidelines to Provide 50 mg./kg./day* for Ventricular Arrhythmias

Ventricular Tachycardia
(give priming dose of 1 g. if patient has not received prior infusion)

Premature Ventricular Contractions



*This dosage schedule is for use as a guide for treating the average patient, but all patients must be considered on an individual basis.

Pronestyl®

Procainamide Hydrochloride)

hrough the entire therapeutic course

See next page for brief summary.

(Procainamide Hydrochloride Tablets)

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

Pronestyl Tablets (Procainamide Hydrochloride Tablets) are veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

Administration: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

How Supplied: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100.

PRONESTYL® INJECTION
(Procainamide Hydrochloride Injection U.S.P.)

Description: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is a sterile aqueous solution providing 100 mg. or 500 mg. procainamide hydrochloride per ml. The 100 mg./ml. potency contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives. The 500 mg./ml. potency contains 0.1% methylparaben and not more than 0.2% sodium bisulfite as preservatives.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. *Intravenous use should be limited to extreme emergencies,* **the drug should be administered as a dilute infusion,** and the patient should be monitored electrocardiographically. The intravenous dose should not exceed 1 gram. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions.

How Supplied: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is available in 10 ml. vials providing 100 mg./ml. and in 2 ml. vials providing 500 mg./ml. ©1974 E. R. SQUIBB & SONS, INC. 444-009

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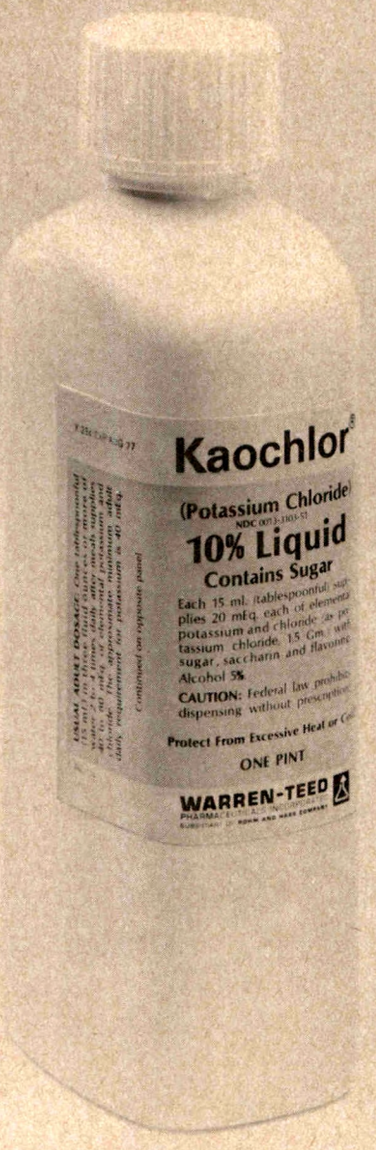

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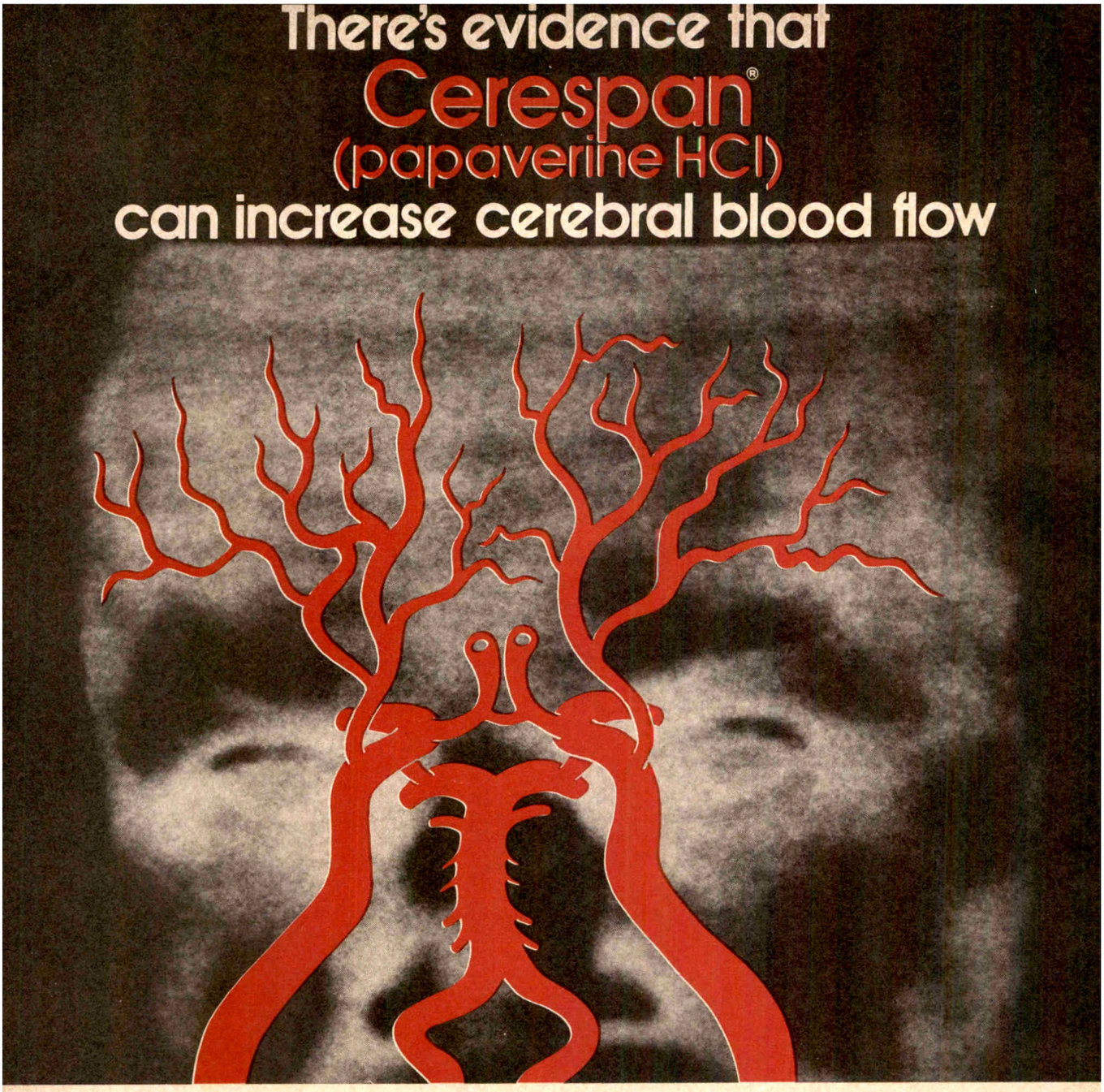

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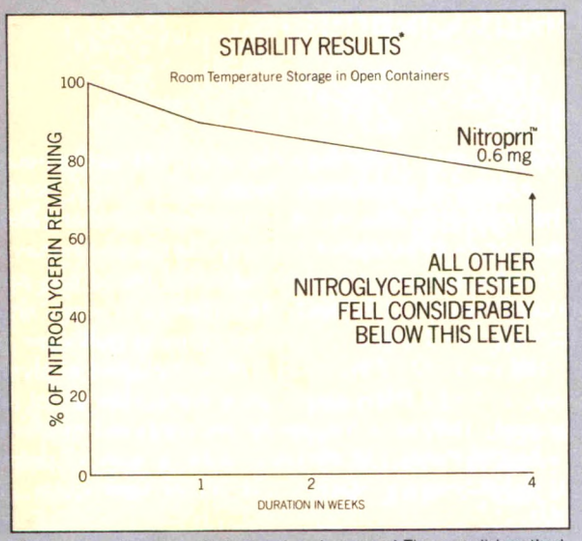

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Survival After Systemic to Pulmonary Arterial Shunts in Infants Less Than 30 Days Old with Obstructive Lesions of the Right Heart Chambers

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Ninety-seven infants less than 30 days old with obstructive lesions of the right heart chambers underwent palliative surgery from 1950 through 1972. The diagnosis was made at cardiac catheterization and confirmed at operation or subsequent autopsy. Because of unavailability of complete preoperative studies and sufficient blood gas data, 36 patients presenting between 1950 and 1965 (Group I) were analyzed for surgical risk only. In 61 patients who underwent palliative procedures between 1966 and 1972 (Group II) a more detailed analysis was done. In this group, 31 had a Potts shunt, 29 a Waterston shunt and 1 a Blalock-Taussig shunt. The most frequently encountered malformation was severe tetralogy of Fallot (30 percent) with or without pulmonary atresia, followed by pulmonary atresia with intact ventricular septum (25 percent).

The overall surgical mortality rate in patients seen after 1965 (Group II) was 34 percent compared with the 78 percent mortality rate in patients seen earlier (Group I). The surgical mortality in infants operated on during the 1st week of life was double that of those operated on in the 2nd through 4th weeks. Survivors were compared with nonsurvivors for timing of surgery, age at presentation and clinical profile. Only two significant differences were found. Preoperative continuous murmurs were more common in those who survived operation (13 of 40 patients) than in those who died (2 of 21). Arterial pH during cardiac catheterization was the best predictor of subsequent survival, nonsurvivors having significantly greater metabolic acidosis. Palliation of these severe lesions still carries a high mortality rate to which must be added the risk of subsequent repair. Our data suggest that primary repair is to be preferred if it can be undertaken with a risk approximating that of palliative procedures.

The increasing success of early corrective surgery in infants for many congenital heart malformations suggested that the results of palliative procedures for obstructive lesions of the right heart chambers should be reevaluated. Surgical attempts to relieve the right ventricular obstruction by infundibulectomy or valvotomy have in the past had a high mortality rate[1,2] except in cases of pure pulmonary valve stenosis with a good-sized right ventricle.[3] When severe enough to produce critical hypoxemia, tetralogy of Fallot, pulmonary atresia, tricuspid atresia and other similar lesions have usually been given palliative treatment with some form of systemic to pulmonary arterial anastomosis.

In this review, we analyze our experience with systemic to pulmonary arterial shunts in newborn infants presenting with various congenital malformations resulting in severe obstruction on the right side of the heart. The early surgical survival rate was related to age at

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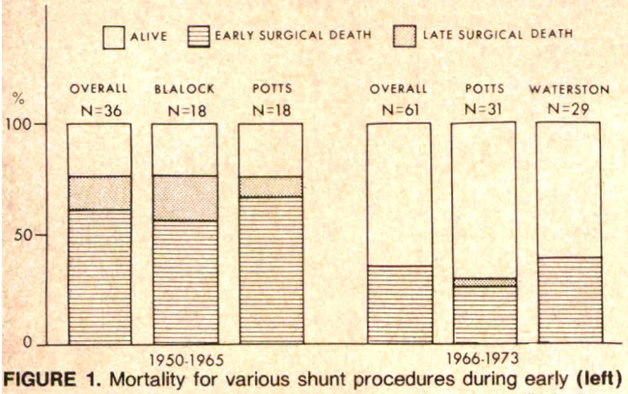

FIGURE 1. Mortality for various shunt procedures during early **(left)** and recent **(right)** years. One patient in the recent group died after a Blalock-Taussig shunt. N = number of patients.

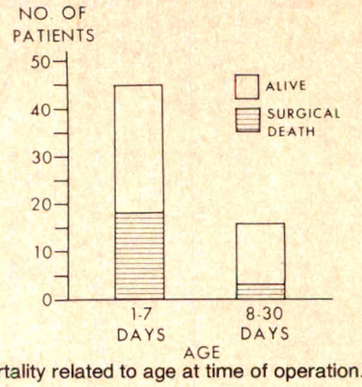

FIGURE 2. Mortality related to age at time of operation.

presentation, severity and type of lesions, timing of operation, type of shunt performed and blood gas status before operation. The late survival of these neonates was also analyzed during the follow-up period.

Materials and Methods

All patients who had a systemic to pulmonary arterial anastomosis as the major palliative procedure and who were 30 days or less of age at the time of operation were included in the study. Between 1950 and 1965 there were 36 patients who underwent shunt procedures of either the Potts or Blalock-Taussig variety (Group I). Between 1966 and 1972 there were 61 patients who had palliative operations, all but one by means of Potts or Waterston shunts. In this latter period we have regarded severe cyanosis with progressive metabolic acidosis despite rigorous correction as an absolute indication for urgent palliation. Patients with severe cyanosis without metabolic acidosis on presentation underwent palliative procedures if acidosis developed or if circumstances excluded close supervision.

In patients of both groups the diagnosis was established by cardiac catheterization and confirmed by subsequent surgery or autopsy. From 1966 through 1972 balloon septostomy was performed during catheterization in patients with transposition of the great arteries and, as previously reported, in those with pulmonary atresia and an intact ventricular septum.[2,4]

Because complete preoperative studies and sufficient blood gas data were not available, patients in Group I were analyzed for surgical risk only; in Group II, a more detailed analysis was done, relating early and late surgical mortality to anatomic diagnosis, age at presentation, timing of operation, type of shunt and acid-base status during cardiac catheterization. Early mortality was defined as that occurring after 1 month but before any further palliative operation. Deaths during the follow-up period were also analyzed.

Values for pH and partial pressures of carbon dioxide ($PaCO_2$) and oxygen (PaO_2) were measured by standard method (Radiometer, Copenhagen) on blood taken from the aorta or femoral artery while the patient was breathing room air during cardiac catheterization.

Results

Group I

Of 36 patients presenting from 1950 through 1965 (Group I), 18 had a Blalock-Taussig anastomosis (subclavian to pulmonary artery) and the remaining 18 patients had a Potts anastomosis (descending aorta to main pulmonary artery). When late mortality was included there was no difference in mortality among patients with two types of shunt, but a higher immediate survival rate was noted with the Blalock-Taussig shunt (Fig. 1).

Group II

The clinical profile of these 61 patients is summarized and data on survivors and nonsurvivors are compared in Table I. There were no significant differences between survivors and nonsurvivors in age at presentation, time of operation, respiratory rate, liver size, blood pressure in the arms, or heart size on chest X-ray film. However, preoperatively the prevalence of continuous murmurs was much greater in those who survived (13 of 40) than in those who died (2 of 21). Furthermore, survivors with such murmurs preoperatively tended to have a higher level of PaO_2 (mean 34 ± 10 [standard deviation] mm Hg) than survivors without such murmurs (mean 28 ± 7). In the two nonsurvivors without such murmurs, the preoperative PaO_2 value was less than 28 mm Hg, suggesting a relatively small level of pulmonary blood flow.

The most frequently encountered malformation was tetralogy of Fallot with pulmonary atresia or severe pulmonary stenosis (18 patients), followed by pulmonary atresia with intact ventricular septum (15 patients) (Table II).

Causes of death: Of 61 patients in Group II, 31 underwent a Potts anastomosis and 29 a Waterston shunt (ascending aorta to right pulmonary artery) (Fig. 1). Only one patient had a Blalock-Taussig shunt. The mortality rate in these patients seen after 1965 was 34 percent compared with 78 percent in those seen earlier (Group I). The mean age at death after operation was 6 ± 8 days. One patient died at age 3 months because of a nonfunctioning shunt. Eight infants were so sick with hypoxia and acidosis that cardiac arrest occurred during induction of anesthesia or during surgery. Ten patients died as a result of a nonfunctioning shunt as judged by continued cyanosis and hypoxia on blood gas analysis and absence of a continuous murmur postoperatively. In only two

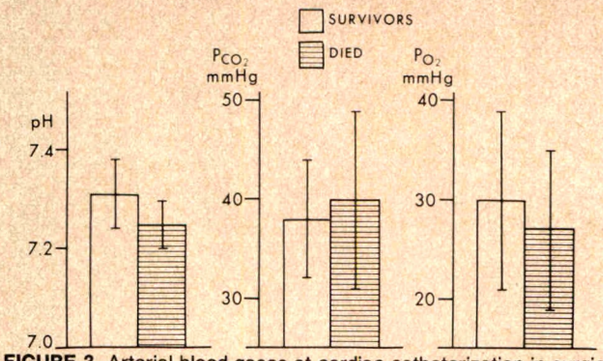

FIGURE 3. Arterial blood gases at cardiac catheterization in surgical survivors and nonsurvivors. There is a statistically significant difference between survivors and nonsurvivors only for pH values ($P < 0.005$).

patients was death considered to be caused by an oversize shunt leading to congestive heart failure and ventilation problems. One patient died of sepsis 7 days postoperatively.

Mortality in neonates: Seventy-four percent of patients in Group II presented during the 1st week of life. The mortality due to shunt surgery in these infants was twice that in infants operated on during the following 3 weeks (Fig. 2). This increased incidence and mortality during the 1st week of life was due to the severity of the specific lesion resulting in early development of hypoxemia. In general, the greater the anatomic complexity of the lesions the higher the mortality rate. Nevertheless, the 18 neonates with tetralogy of Fallot had the second highest mortality rate in the group (Table III). These cases, presenting so early in life, represent the most severe form of tetralogy of Fallot; 7 of the 18 infants had pulmonary atresia, and the 11 others had severe infundibular or pulmonary valve stenosis, or both. One cannot compare mortality rates due to the Potts and Waterston shunts because of our bias for a particular shunt procedure for a specific lesion. For example, a Potts shunt was preferred for pulmonary atresia with intact ventricular septum and a Waterston shunt for tetralogy of Fallot.

Late survival: The single most predictive indicator of survival was the blood gas analysis performed at the time of cardiac catheterization. The nonsurvivors had a significantly higher degree of metabolic acidosis (Fig. 3). Both survivors and nonsurvivors had moderate to severe hypoxemia (difference between groups not significant) and $PaCO_2$ levels were comparable in both groups. Of the 40 survivors 37 are still alive. Two patients with pulmonary atresia and an intact septum died at age 14 and 17 months, respectively, after pulmonary valvotomy undertaken with the hope of promoting right ventricular growth. One patient died suddenly at home at age 10 months from an unknown cause. The shunts were judged to be functioning satisfactorily in all but one patient who required a Blalock-Taussig shunt at age 27 months. This patient has a single ventricle with pulmonary atresia. Two patients have undergone com-

TABLE I

Preoperative Clinical Profile of Survivors and Nonsurvivors in Group II (mean ± standard deviation)

	Survivors (no. = 40)	Nonsurvivors (no. = 21)
Respiratory rate/min	55 ± 18	58 ± 23
Liver size (cm)	1.7 ± 0.98	2.0 ± 1.0
Systolic blood pressure in arms (mm·Hg)	77 ± 18	78 ± 10
Continuous murmur due to patent ductus arteriosus	13 of 40	2 of 21
Cardiothoracic ratio on chest X-ray film (%)	56 ± 6	54 ± 7
Age at admission (days)	4.0 ± 5	4.0 ± 6
Age at operation (days)	6 ± 6	6.0 ± 8
Time of death after operation (days)	. . .	6.0 ± 7*

*One late death at age 3 months is included.

TABLE II

Anatomic Diagnosis and Surgical Mortality in Group II

	Frequency		Mortality*	
	no.	%	no.	%
Tetralogy of Fallot†	18	29.5	7	39
Pulmonary atresia with intact ventricular septum	15	24.6	4	27
Single ventricle	8	13.1	2	25
Tricuspid atresia	9	14.8	2	22
d transposition of great vessels	4	6.5	2	50
Miscellaneous combined lesions‡	7	11.5	4	57
Total	61	100	21	34

*Deaths due to palliation during neonatal period and to any further palliative procedure.

†All patients with tetralogy of Fallot had severe pulmonary stenosis or atresia. Seven of the 18 had pulmonary atresia, and 3 of these died.

‡Dextrocardia, pulmonary atresia, patent ductus arteriosus, tricuspid atresia and single ventricle (one patient); asplenia syndrome (two patients); levocardia situs inversus, pulmonary atresia, total anomalous pulmonary venous drainage and left superior vena cava (one patient); hypoplastic right ventricle and tricuspid stenosis (one patient); transposition of great vessels with pulmonary atresia (one patient); and pulmonary valve stenosis with intact ventricular septum (one patient).

TABLE III

Type of Shunt and Diagnosis in Surgical Survivors (Group II)

	Type of Shunt	
	Waterston	Potts
Tetralogy	10 of 17	1 of 1
Pulmonary atresia	1 of 1	11 of 14
Single ventricle	4 of 5	2 of 3
Tricuspid atresia	2 of 3	5 of 6
Transposition of great arteries	0 of 1	1 of 3
Miscellaneous	1 of 2	2 of 4
Totals	18 of 29	22 of 31

TABLE IV

Survival After Systemic to Pulmonary Arterial Shunts in Neonates (1966 to 1974)

	Patients with Shunt (no.)	Survivors (no.)	Mean Follow-Up (mo.)
Tetralogy of Fallot	18	11	31
Pulmonary atresia with intact ventricular septum	15	9	42
Single ventricle	8	6	49
Tricuspid atresia	9	6	37
d Transposition of great arteries	4	2	53
Miscellaneous	7	3	27
Totals	61	37	40

plete repair of tetralogy and one patient with pulmonary atresia and an intact septum has had successful replacement of both tricuspid and pulmonary valves (Table IV).

Discussion

Palliative procedures in infants with critically obstructive lesions of the right heart chambers have been associated with a high surgical mortality rate[5–8] although improvement has occurred in recent years.[9–11] This review indicates that in our recent experience the surgical mortality rate has been more than halved. Several factors have contributed to this reduction including earlier referral, earlier and more precise diagnosis, improved surgical and anesthetic expertise and better postoperative care. The metabolic consequences of severe hypoxemia have also been better appreciated.

The timing of surgery after cardiac catheterization might have influenced the surgical results. However, there was no significant difference between the survivors and nonsurvivors in respect to age at admission or at operation.

Metabolic acidosis and hypoxemia: A severe reduction in arterial PaO_2 results in metabolic acidosis due to tissue hypoxemia and lactic acidemia.[12–14] Hypoxemia and metabolic acidosis, either alone[15] or in concert,[16] impair myocardial performance by direct action on the myocardium and by decreasing the myocardial responsiveness to catecholamines.[15] This leads to a further decrease in both pulmonary blood flow and peripheral perfusion resulting in increasing tissue hypoxemia that, in turn, accelerates the acidosis and establishes a rapidly progressive vicious cycle. Hypothermia caused metabolic acidosis[17,18] by increasing the excess acid in the extracellular fluid. Normal infants respond to hypothermia by increasing their metabolic rate, as shown by an increased oxygen consumption.[19] Hypoxemia reduces the infant's ability to increase oxygen consumption[20] and therefore impairs his compensatory response to cold stress. Thus, in the hypoxemic infant hypothermia develops more easily, is poorly tolerated and compounds the existing metabolic acidosis. The rapidity with which this situation develops depends upon the severity of right heart obstruction and on the pulmonary blood flow including collateral blood supply to the lungs.

Our study showed that the single most significant factor in predicting the outcome of palliation is the degree of metabolic acidosis at cardiac catheterization. The development of metabolic acidosis is related in part to the severity of the lesion. The presence of a patent ductus arteriosus increases pulmonary blood flow and thus results in a lesser degree of metabolic acidosis. This is reflected in our study by a significantly higher prevalence of patent ductus arteriosus and a tendency toward higher PaO_2 levels in those surviving palliation, this group showing a lesser degree of metabolic acidosis. It seems likely that the improvement of metabolic status, and better preoperative temperature control should further improve the surgical results of palliation.

Medical management: Nearly all the patients in Group II received respiratory assistance immediately after surgery, and this has undoubtedly been a major factor in the improved surgical results. Acidosis should be corrected with sodium bicarbonate in appropriate doses. The role of isoproterenol in these patients requires evaluation. Theoretically, it may be beneficial in several respects. By its positive inotropic action on the myocardium, it should result in improved cardiac output, which, combined with its vasodilatory effects on both pulmonary and systemic vasculature, should increase pulmonary and systemic blood flow and oxygen delivery to the tissues.

Surgical management: Over the years we have evolved a certain policy for each malformation within this group of lesions. Pulmonary atresia with an intact ventricular septum is managed by combining balloon atrial septostomy with a Potts anastomosis[2–4] and pulmonary valvotomy where possible, whereas the Waterston shunt is used in tetralogy of Fallot. The Blalock-Taussig shunt has been abandoned because of the high mortality rate associated with this procedure, probably due to failure to achieve an adequate shunt. Infant survival rates after shunt surgery for tetralogy of Fallot have been low in the reported experience.[11,21–24] The mortality rate for palliation in cases of tetralogy of Fallot in this review is 39 percent and, although these are the severest cases of tetralogy, many are potentially correctable. The advent of surface cooling and deep hypothermia now provides an alternative approach of primary repair in these patients.[25–27] If primary correction can be achieved with a mortality comparable to that of palliation then this would be preferable even though the long-term result of primary repair in the 1st month of life is unknown.

Pulmonary atresia, tricuspid atresia and single ventricle with pulmonary stenosis are unlikely to be amenable to reparative surgery in the young infant in the near future and will continue to require palliation. Optimal results in these patients can be achieved only by early referral and investigation, meticulous attention to their acid-base status and early palliative surgery.

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Results of Pulmonary Arterial Banding in Infancy

Survey of 5 Years' Experience in the New England Regional Infant Cardiac Program

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LUCY PARISI-BUCKLEY, MD
DONALD C. FYLER, MD
ALEXANDER S. NADAS, MD

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The results of pulmonary arterial banding in 238 infants, 12 percent of the infants admitted to the New England Regional Infant Cardiac Program, is reviewed. Overall survival to age 1 year was 63 percent. Survival was least likely (37 percent) in those who required banding within the 1st month of life. Additional surgery decreased the survival rate in those operated on after 1 month of age. Infants with anomalies for which no corrective surgical procedure is available (23 of 238) have only a 30 percent chance of survival. Those with lesions correctable within the 1st year (133 of 238) have a 74 percent survival rate; 52 percent (82 of 238) of those for whom a curative operation is available after the 1st year survive. These pulmonary arterial banding data coupled with results of primary correction should provide the data base required for an intelligent decision in respect to appropriate surgical treatment of infants with critical heart disease.

In 1952, Damman and Muller[1] introduced pulmonary arterial banding in patients with a ventricular septal defect as a palliative procedure to decrease pulmonary blood flow and pressure. Since that time, the procedure has been used effectively in various congenital cardiac lesions, the majority of which are potentially correctable today. Because surgical management at present is changing from providing palliation to performing early, primary repair, the relative risk of these two approaches requires careful evaluation. For this reason, we have reviewed the 5 year experience (1968 to 1973) with pulmonary arterial banding in all patients under 1 year of age in the New England Regional Infant Cardiac Program. This program, which began in 1968, includes all infants born with congenital heart disease in New England who undergo cardiac catheterization, cardiac surgery or die within the 1st year of life and encompasses 11 centers (Table I) with facilities for diagnosing and treating these infants. It is hoped that by evaluating the clinical course of all patients in one region who underwent pulmonary arterial banding in several institutions with various facilities, the true effectiveness of the procedure may be better assessed than by surveying the limited and selective experience of one institution.

Methods

The mechanics for computerized data collection and coding of all infants with cardiac disease in the program were described by Fyler et al.[2] in 1972. This review includes all patients undergoing pulmonary arterial banding in the 1st year of life irrespective of type of lesion, presence of low birth weight or major associated anomalies.

Survival to age 1 year was assessed by diagnosis, age at pulmonary arterial banding and influence of other surgical procedures at the time of banding. Relatively rigid criteria are used to assign each patient to major diagnostic categories, the relative frequency of which have remained constant over 5 years of data collection.

Arbitrarily, patients are classified into those with potentially correctable

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and currently uncorrectable lesions. Although such a division may be controversial, it is nonetheless useful for our purposes, particularly if one confines "correctable" lesions to those in which there have been published reports of successful total repair.

Patients with potentially correctable lesions are further classified into those in whom corrective procedures are being accomplished before 1 year of age and those in whom surgical correction is performed only after 1 year of age.

The decision to palliate with pulmonary arterial banding was based on the individual judgment of pediatric cardiologists in the 11 centers. The indications included congestive heart failure not responding to medical management and prevention of development of pulmonary vascular obstructive disease.

Results

The 5 year experience (July 1968 to June 1973) of the New England Regional Cardiac Program includes a total of 1,916 patients. Twelve percent (238) of these have undergone pulmonary arterial banding. Irrespective of diagnosis the overall survival rate to age 1 year was 63 percent. Included in the total number of 238 are 7 who died at the time of "total correction" and another 7 who died of unrelated causes such as pneumonia or aspiration.

Associated noncardiac anomalies: Patients with severe associated noncardiac anomalies and low birth weight were analyzed separately to determine whether these factors influenced survival. Among the 19 patients with associated anomalies (8 with mongolism, 5 with central nervous system disorders, 2 with rubella syndrome, and 4 with genitourinary or renal disorders), the survival rate was 63 percent (12 of 19). Among the 21 infants with low birth weight (range 1.44 to 2.25 kg), the overall survival rate was 57 percent (12 of 21). Since the survival rate of both these groups compares favorably with the total patient experience, hereafter they are included in the overall results.

Age of banding: In Table II, the patients are classified by age at the time of pulmonary arterial banding. Those who underwent banding at less than 1 month of age have the poorest survival rate (37 percent), probably because these infants tend to be more ill and often have more complex lesions.

Banding alone or combined with other procedures: In Table III, survival data in patients who underwent pulmonary arterial banding alone is compared with survival in infants in whom banding was combined with other surgical procedures (atrial septectomy, patent ductus arteriosus ligation or division, resection of coarctation). Infants who underwent banding alone had an overall survival rate of 76 percent; those with combined banding and other surgical procedures had an overall survival rate of 51 percent. A distinct relation between age at operation and survival is again noted, although the additional surgical procedure does not seem to influence the already poor survival rate in the group operated upon before 1 month of age.

Correctable vs. uncorrectable lesions: The various lesions are divided into those potentially correctable and uncorrectable in Table IV; 90 percent of patients (215 of 238) had potentially correctable lesions, and more than half of these lesions were correctable within the 1st year of life. Survival to 1 year of age (Table V) was greatest (74 percent) among infants with lesions correctable before age 1 year (ventricular septal defect with normally related or dextrotransposed great arteries). Survival decreased to 52 percent in patients with more complex lesions poten-

TABLE I

New England Regional Infant Cardiac Program: Participating Centers

Center and Physician	City and State
Hartford Hospital Leon Chameides, MD	Hartford, Conn.
St. Francis Hospital Ellen Marmer, MD	Hartford, Conn.
Yale-New Haven Hospital Norman S. Talner, MD	New Haven, Conn.
Maine Medical Center Edward C. Matthews, MD	Portland, Maine
Tufts-New England Medical Center Hospital Boston Floating Hospital for Infants & Children Marshall B. Kreidberg, MD	Boston, Mass.
Children's Hospital Medical Center Donald C. Fyler, MD	Boston, Mass.
Massachusetts General Hospital Allan Goldblatt, MD	Boston, Mass.
Dartmouth-Hitchcock Medical Center Richard J. Waters, MD	Hanover, N.H.
Rhode Island Hospital Robert D. Corwin, MD	Providence, R.I.
Medical Center Hospital of Vermont Mary Fletcher Unit Arthur M. Levy, MD	Burlington, Vt.

TABLE II

Survival to Age 1 Year by Age at Banding

Age at Surgery	Patients	Patients Surviving
0–30 days	54	20(37%)
31–90 days	75	45(60%)
3–12 months	109	84(77%)
Total	238	149(63%)

TABLE III

Survival to Age 1 Year by Type of Operation

Procedure	Total Patients	Survivors Operated on at Age <1 Month	Survivors Operated on at Age 1–<3 Months	Survivors Operated on at Age 3–12 Months	Total Survivors
Banding alone	111	5/13 (38%)	22/31 (71%)	57/67 (85%)	84 (76%)
Banding and other*	127	15/41 (37%)	23/44 (53%)	27/42 (64%)	65 (51%)
Total	238	20/54 (37%)	45/75 (58%)	84/109 (77%)	149 (63%)

* Creation of an atrial septal defect, ligation of patent ductus arteriosus or coarctation resection.

TABLE IV

Nature of Banded Defects

Defect	Patients (no.)
Potentially Correctable Lesions	
Correctable within 1st year	133 (56%)
Ventricular septal defect	
Simple	51
Complex	49
Dextrotransposition of great arteries + ventricular septal defect	33
Correctable after 1st year	82 (34%)
Single ventricle	20
Atrioventricular canal	19
Truncus arteriosus	15
Double outlet right ventricle	11
Complex coarctation of aorta	10
Levotransposition of great arteries + ventricular septal defect	5
Tricuspid atresia	2
Currently Uncorrectable Lesions	
Hypoplastic left heart	17
Complex malposition	6 (10%)
Total	238 (100%)

Figures in parentheses indicate percent of distribution within category.

TABLE V

Survival to Age 1 Year by Nature of Defects

Defect	Patients	Patients Surviving
Correctable within 1st year	133	99 (74%)
Correctable after 1st year	82	43 (52%)
Currently uncorrectable	23	7 (30%)
Total	238	149 (63%)

tially correctable only after 1 year of age (single ventricle, atrioventricular canal, double outlet right ventricle, truncus arteriosus, corrected transposition of great arteries, complex coarctations, tricuspid atresia). Among the small group in whom total repair was not feasible only 30 percent survived with palliation. If one considers the survival data in terms of anatomy, the group with simple ventricular septal defect had, as expected, the highest survival rate (92 percent) (Table VI). Those with a complex ventricular septal defect (that is, defect with patent ductus or coarctation) requiring additional surgical procedures had a poorer survival rate (67 percent) as did those with dextrotransposition of great arteries (58 percent). Among patients with lesions correctable after age 1 year the best results were seen in patients with double outlet right ventricle (82 percent survival), whereas those with truncus arteriosus (33 percent) and complex coarctations (40 percent) had poorer results (Table VIB). The 23 patients with uncorrectable lesions (10 percent of all patients with pulmonary arterial banding), including those with hypoplastic left heart syndrome and complex malpositions (heterotaxy syndrome and dextrocardia with complex

TABLE VI

Survival to Age 1 Year In Patients with Potentially Correctable Lesions

Defect	Patients (no.)	Survival
A. Lesion Potentially Correctable Within 1st Year		
Ventricular septal defect		
Simple	51	47 (92%)
Complex	49	33 (67%)
Total	100	80 (80%)
Dextrotransposition of great arteries + ventricular septal defect		
Banding +/– balloon atrial septectomy	7	5 (71%)
Band + other surgery*	26	14 (54%)
Total	33	19 (58%)
Overall	133	99 (74%)
B. Lesion Potentially Correctable After 1st Year		
Single ventricle	20	11 (55%)
Atrioventricular canal	19†	10 (53%)
Truncus arteriosus	15	5 (33%)
Double outlet right ventricle	11	9 (82%)
Complex coarctation	10	4 (40%)
Levotransposition of great arteries	5	3 (60%)
Tricuspid atresia	2	1 (50%)
Total	82	43 (52%)

* Creation of atrial septal defect; ligation of patent ductus arteriosus.

† Includes 8 patients with mongolism, 3 surviving. With elimination of these data the corrected survival rate is 64 percent.

anatomy) had uniformly poor results (30 percent survival rate).

Table VII shows survival to 1 year of age as determined by operability of lesion, age at pulmonary arterial banding and addition of other surgical procedures. Clearly, the younger infants with the more complex lesions who underwent banding in combination with other surgical procedures had the poorest survival rates. Conversely, the somewhat older patients (1 to 3 months) who had a lesion potentially correctable within the 1st year and who underwent banding alone had the best results.

Discussion

Experience with pulmonary arterial banding as a palliative procedure for lesions with high levels of pulmonary blood flow and pressure has advanced considerably since the procedure was first described in 1952. Numerous reports have described both the advantages and complications, and the results of several large series[3–5] have been comparable with ours. The overall survival rate after pulmonary arterial banding in infants with complex congenital heart disease has been reported[6] to be 68 percent (41 of 60), somewhat higher than our 52 percent rate (43 of 82). Poor survival in this group, as in our experience, was related to performance of surgery at an early age.

Since 11 different centers are providing data for our patient pool, which represents at least 80 percent of the infants with serious cardiac lesions in New En-

TABLE VII

Survival by Lesion and Age at Banding

	Banding at 0–1 Month		Banding at 1–3 Months		Banding at 4–12 Months		Total	
	T	S	T	S	T	S	T	S
Lesion potentially correctable								
Within 1st year								
Banding	3	2	11	9	45	42	59	53(89.8%)
Banding + other procedure	20	8	27	17	27	21	74	46(62.1%)
Total	23	10(42%)	38	26(68%)	72	63(88%)	133	99(74%)
After 1st year								
Banding	8	2	14	9	22	15	44	26(59%)
Banding + other procedure	15	6	13	6	10	5	38	17(44.6%)
Total	23	8(36%)	27	15(56%)	32	20(63%)	82	43(52%)
Uncorrectable								
Palliate/uncorrectable								
Banding	2	1	6	4	0	0	8	5
Banding + other procedure	6	1	4	0	5	1	15	2
Total	8	2	10	4	5	1	23	7(31%)
Overall total	54	20(37%)	75	45(58%)	109	84(77%)	238	149(62.6%)

S = survivors; T = total number of patients.

gland,[7] these results are unique and may be used to assess results in other areas of the country. Comparable data from other regions are unavailable at present.

Indications for banding in uncorrectable defects: The infants with banding in our series included patients with a variety of lesions, only 10 percent of which are presently considered uncorrectable. The survival data in this group with uncorrectable lesions was poor; less than one third reached their 1st birthday. Therefore, we do not recommend with great enthusiasm pulmonary arterial banding in this group of patients, since the survival rate of those with banding is poor and complete correction is not possible.

Indications for banding in defects potentially correctable after the 1st year of life: Of great interest are infants with defects potentially correctable after the 1st year of life (82 of 238). They had a 52 percent overall survival rate, with the 11 patients with double outlet right ventricle having an 82 percent survival rate. Hartmann et al.[8] also reported that patients with this lesion, particularly those with a subpulmonary ventricular septal defect, derived considerable benefit from banding. Khattri et al.[9] showed that long-term survival of patients with double outlet right ventricle and valvular pulmonary stenosis was considerably better than in those without pulmonary stenosis. The 19 patients with atrioventricular canal, approximately one quarter of the group with banding and a lesion potentially correctable after 1 year of age, had a survival rate of 53 percent; if one eliminates data on the eight patients with mongolism, the survival rate increases to 64 percent. Utley[10] has shown that many factors influence the outcome of banding in atrioventricular canal. They postulate that banding in this lesion, although beneficial in decreasing pulmonary arterial pressure and reducing work of breathing, may actually worsen congestive heart failure by increasing right ventricular afterload and tricuspid regurgitation. Patients with significant mitral regurgitation may also show deterioration after banding.

In view of the rapid advances in corrective surgery and the relatively favorable survival data in this group as a whole, we recommend that all patients in this category, especially those with atrioventricular canal and double outlet right ventricle, who exhibit congestive heart failure or pulmonary arterial hypertension undergo pulmonary arterial banding in early infancy.

Indications for banding in defects correctable in 1st year of life: Finally, in patients with defects correctable within the 1st year of life, the survival rate with banding was an acceptable 74 percent (92 percent for infants with a simple ventricular septal defect). It is in this same large group of patients that the impetus for early surgical correction is greatest. Castenada[11] has reported a survival rate of 92 percent (34 of 37) using deep hypothermia for primary repair in infants with a ventricular septal defect, although two of these patients required simultaneous pulmonary arterial banding because of incomplete closure of the defect noted at surgery. The use of hypothermia began subsequent to the collection period for this report. Although primary correction avoids the jeopardy of two surgical procedures, and the economic and psychological problems inherent in two cardiac operations, definitive proof of its relative merit over the procedures of primary banding and secondary correction is still awaited. The data reported here provide a base line for comparison with results of primary repair. Pulmonary arterial banding in patients with a complex ventricular septal defect (associated atrial septal defect, patent ductus arteriosus or coarctation of aorta) had a poorer survival rate (67 percent), reflecting in most instances sicker infants and the hazard of additional surgical procedures. Identification of associated lesions is difficult

but mandatory since banding alone may not improve the condition of these infants and may even hasten deterioration.

Indications for banding in dextrotransposition of great arteries and ventricular septal defect: Patients with dextrotransposition of great arteries and ventricular septal defect had a 71 percent survival rate; this decreased, however, to 54 percent if additional surgery (patent ductus ligation or atrial septectomy) was necessary. Waldhausen et al.[12] reported a higher survival rate (70 percent) in a small series of patients having surgical atrial septectomy and banding. Ferencz[13] reviewed the microscopic lung sections of 106 patients with dextrotransposition of great arteries and ventricular septal defect and found grade 3-4 vascular changes (Heath and Edwards' classification) present in patients as early as age 6 months. Plauth et al.[14] showed that pulmonary vascular obstruction developed as early as age 3 months with an average of 5 1/2 years in the patients they studied. Newfeld et al.[15] showed that in patients with this lesion grade 3-4 changes may be seen as early as age 6 months and is the rule after 1 year. In view of these data indicating the inevitability of early pulmonary vascular obstructive changes in this group, surgical intervention before age 6 months is mandatory. The very poor survival rates after "primary correction" in most centers in infants less than 1 month old make banding the operation of choice in the neonate although the results are far from optimal. Whether "primary correction" or banding should be the procedure of choice between the neonatal period and age 6 months is not known. Breckenridge et al.[16] reported repair before age 1 year in nine patients with transposition of great arteries and ventricular septal defect. Between 1967 and 1970 none of four patients who underwent correction survived, whereas in 1971 five corrections were attempted with four survivors. If the patient's clinical condition allows conservative treatment to age 6 months, then total correction is the plan of choice today.

Present surgical recommendations: Considering present day results of cardiac surgery, the following suggestions may be reasonable:

1. Pulmonary arterial banding in the group with currently totally uncorrectable lesions is not recommended except in unusual circumstances (that is, symptomatic relief when there is a possibility of a long survival time).

2. Early pulmonary arterial banding is the procedure of choice for infants with defects presently correctable after age 1 year, since it offers the only hope for later correction.

3. Pulmonary arterial banding is an acceptable palliative operation for patients with a large ventricular septal defect, with or without transposition of the great arteries, in institutions that do not have a large patient volume and extensive experience in infant cardiovascular surgery. In the large centers with pediatric cardiology and cardiovascular surgery teams, primary correction is probably, but not unquestionably, preferable. Patients with a large ventricular septal defect, particularly those with transposition of the great arteries, should have palliative or corrective surgery within the first 6 months of life, if long-term survival is desired.

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Considerations in the Surgical Management of Infantile Coarctation of Aorta

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The results of a recent 5 year experience with resection of coarctation of the aorta in infants less than 1 year of age are compared with those of an earlier series from the same institution. The significant improvement in mortality and morbidity statistics is attributed to modifications in operative and postoperative care. Operative mortality has decreased from 38 to 17 percent and the incidence rate of significant restenosis has diminished from 60 to 33 percent. It is suggested that in patients with a large associated intracardiac shunt banding of the main pulmonary artery should be performed before resection of the coarctation. Three of five patients have survived procedures performed in this sequence. Microsurgical techniques and careful approximation of the aortic lumen with interrupted sutures are the major factors responsible for the reduced incidence of recoarctation. Prolonged ventilatory support postoperatively with the occasional addition of controlled positive airway pressure and continued aggressive medical therapy for heart failure are recommended.

Surgical resection of coarctation of the aorta in infants less than 1 year of age remains a challenging endeavor. Nevertheless, there is general agreement that children with uncontrolled congestive heart failure despite aggressive medical management should undergo coarctectomy.[1–5] Factors that unfavorably influence the results in these infants include the degree of left ventricular failure and the presence of severe intracardiac and extracardiac vascular anomalies. It is well established therefore that preparation for resection should include aggressive therapy with digitalis and diuretic agents along with cardiac catheterization and accurate assessment of the associated anomalies. Acceptable mortality figures have ranged between 25 and 45 percent.[1,4,6–8] The operative mortality rate in the initial series of patients from this institution was 36 percent (Table I). This report describes the improved results achieved in the last 5 years and attempts to define responsible modifications in the operative and postoperative care of these children.

Large cardiac shunts at the ventricular level are among the more common lesions associated with infantile coarctation, and banding of the main pulmonary artery should be carried out at the time of resection.[4,9,10] However, with the initial excision of the coarctation, clamping of the aorta will increase the impedance to aortic flow which, in the absence of an intraventricular gradient, will increase pulmonary blood flow and, hence, left ventricular diastolic filling. Thus, an excessively afterloaded left ventricle becomes also excessively volume loaded and the result may be acute intraoperative left ventricular failure. We therefore contend that the band should be applied before coarctectomy. The maintenance of aggressive medical therapy and strict attention to ventilatory support in the postoperative period are suggested as further reasons for the improvement in survival rates.

The development of stenosis at the site of resection, recreating the

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pathophysiologic features of coarctation, probably occurs as a consequence of several factors.[11–14] Our recent adaptation of microsurgical techniques similar to those utilized in coronary arterial surgery has significantly diminished the frequency of this complication. With the development of hemodynamically significant stenosis after resection, all patients have remained asymptomatic with medical therapy. The management of recurrent coarctation is safe and effective, and therefore apprehension concerning this complication should not delay the initial procedure in these young children.[11]

Surgical Methods

Operative procedures: The coarcted segment was exposed through a left posterior thoracotomy. The third interspace was entered. The pleura overlying the distal arch and proximal descending aorta was incised longitudinally with reflection medially and laterally. The left subclavian artery, distal arch and descending thoracic aorta proximal and distal to the coarctation were looped with tapes. Care was taken to preserve all distal collateral vessels.

If catheterization data revealed a large intracardiac shunt with equal systemic and pulmonary arterial pressures, a banding procedure on the main pulmonary artery was performed. The pericardium was opened longitudinally anterior to the left phrenic nerve and the band applied until there was a sustained increase in aortic pressure. A patent ductus arteriosus or ligament was triply ligated. Small coarctation clamps were applied and the involved segment excised. An end to end anastomosis was accomplished in all cases. Frequently the proximal lumen included the origin of the left subclavian artery so that the two aortic ends were nearly equal in size. The anastomoses were carried out with 7-0 and 8-0 suture material in interrupted fashion.

Postoperative management: This involved careful attention to ventilatory support as well as continued aggressive therapy of the congestive heart failure. Often these children received respiratory support for 24 to 72 hours, with frequent monitoring of their arterial blood gases. When pulmonary congestion and associated pneumonia developed, controlled positive airway pressure was added to the ventilatory support regimen to improve arterial oxygen saturation. All patients received postoperative antibiotic therapy, usually ampicillin, 11 mg/kg body weight, and kanamycin, 15 mg/kg intramuscularly in divided doses.

Results

During the past 5 years, 18 children less than 1 year of age with coarctation of the aorta and associated heart failure were operated upon (Table II). Nine patients were less than 2 weeks of age and the smallest child weighed 1,100 g. Sixteen patients (89 percent) had severe additional intracardiac and extracardiac vascular anomalies, with five patients (28 percent) requiring pulmonary arterial banding at the time of resection (Table I).

Mortality: There were no intraoperative deaths. Two early deaths (Cases 1 and 6) occurred at 12 and 14 hours postoperatively. Both infants died with profound cardiac failure. One patient had corrected transposition of the great vessels with atrioventricular communis and underwent banding at the time of resection. The second child had aortic valvular stenosis and an atretic aortic arch. A late death occurred 31 days postoperatively in a patient (Case 8) with a secundum atrial septal defect, large ventricular septal defect and hypoplastic left ventricle. This patient also had a pulmonary arterial banding as well. The other children who underwent pulmonary arterial banding in association with coarctectomy survived (Table II).

TABLE I

Results of Surgical Resection for Coarctation of Aorta (1960–66 and 1969–74)

	1960–66	1969–74
Patients (no.)	14	18
Age range	2 days to 11 months	2 days to 1 year
Incidence of associated cardiac malformations	12 of 14 (86%)	16 of 18 (89%)
Incidence of pulmonary arterial banding in association with coarctectomy	0 of 14 (0%)	5 of 18 (28%)
Early mortality	4 of 14 (29%)	2 of 18 (12%)
Late mortality	1 of 14 (7%)	1 of 18 (5%)

Follow-up: Information is available on all 15 survival patients (Table III). The majority have had Doppler blood pressure measurements. Five patients (36 percent) have a significant gradient of 20 mm Hg or more between the upper and lower limbs. Only one patient (Case 2) has significant hypertension in the arms, but she remains asymptomatic with medical therapy.

Comments

Infants with coarctation of the aorta and congestive heart failure present challenging problems to all involved in their care. More than 75 percent of these children have severe associated cardiac or great vessel anomalies which by reason of shunt or obstructive phenomena place added strain upon the left ventricle.[7,9,15,19] Among the most common abnormal cardiac communications are ventricular septal defect and persistent common atrioventricular (A-V) canal. Becker et al.[9] reported that 36 percent of their cases had these lesions. Tubular hypoplasia of the aorta, underdevelopment of the left heart chambers and obstructive lesions involving the mitral valve and left ventricular outflow tract are often described. Endocardial fibroelastosis is frequently associated with and considered to be secondary to coarctation of the aorta, severe aortic stenosis or aortic atresia.[16]

When these severe anomalies are present attempts at medical management alone are understandably disastrous and, indeed, surgical intervention is often futile. There is little doubt that the more advanced the anomaly, the worse the prognosis, whatever the treatment regimen. The mortality rate associated with surgical resection has ranged between 25 and 45 percent. The results in a group of infants operated upon in an earlier era at our institution were not dissimilar. These figures represent considerable im-

TABLE II

Coexisting Cardiac Anomalies and Results of Surgery for Coarctation of Aorta (1969–74)

Case no.	Age at Operation	Anatomic Diagnosis	Operation	Result
1	2 days	Coarctation, VSD, ASD, hypoplasia of ascending aorta	Coarctectomy	Early death
2	3 days	Coarctation, PDA	Coarctectomy (1,100 g wt)	Alive and well
3	5 days	Coarctation, ASD, VSD, PDA	PA banding, coarctectomy	Alive and well
4	7 days	Coarctation, VSD, PDA	PA banding, coarctectomy	Alive and well
5	9 days	Coarctation, ASD	Coarctectomy	Alive and well
6	10 days	Coarctation, corrected TGV, A-V canal	PA banding, coarctectomy	Early death
7	2 weeks	Coarctation, PDA	Coarctectomy	Alive and well
8	2 weeks	Coarctation, ASD, VSD, LV hypoplasia	PA banding, coarctectomy	Late death
9	2 weeks	Coarctation, pulmonary hypertension	Coarctectomy	Alive and well
10	3 weeks	Coarctation, VSD	Coarctectomy (1,500 g wt)	Alive and well
11	1 month	Coarctation, VSD	PA banding, coarctectomy	Alive and well
12	4 months	Coarctation, EFE	Coarctectomy	Alive and well
13	5 months	Coarctation, PDA, EFE	Coarctectomy	Alive and well
14	1 year	Coarctation, EFE	Coarctectomy	Alive and well
15	1 year	Coarctation, PDA	Coarctectomy	Alive and well
16	3 months	Coarctation	Coarctectomy	Alive and well
17	4 months	Coarctation, EFE	Coarctectomy	Alive and well
18	7 days	Coarctation, ASD	Coarctectomy	Alive and well

ASD = atrial septal defect; A-V = atrioventricular; EFE = endocardial fibroelastosis; LV = left ventricular; PA = pulmonary arterial; PDA = patent ductus arteriosus; TGV = transposition of the great vessels; VSD = ventricular septal defect; wt = weight.

TABLE III

Follow-Up of Patients (1969–74)

Case no.	Age at Resection (mo)	Length of Follow-Up (mo)	Pressure Gradient Between Upper and Lower Limbs (mm Hg)
2	3	2	None
3	1 wk	22	28 (110/92; 82/60)
4	1 wk	37	None
5	2 wk	37	66 (136/104; 70/0)
7	2 wk	21	14 (104/90; 90/40)
9	2 wk	34	44 (126/90; 82/60)
10	3 wk	36	50 (145/90; 95/0)
11	1	12	None
12	4	23	None
13	12	37	12 (11/84; 98/80)
14	5	30	14 (112/80; 98/84)
15	3	2	None
16	3	2	None
17	4	3	None
18	1 wk	2	None

provement over medical therapy alone since most of these ill children die without surgical intervention. Recent modifications in our operative and postoperative technique have contributed to further improvement in the statistics.

Indications for and timing of pulmonary arterial banding: Many of these children have a large ventricular septal defect or severe endocardial cushion defect with pulmonary overcirculation and hypertension. Areas of major concern therefore are the indications for and timing of pulmonary arterial banding. Any child with a large intracardiac left to right shunt whose ventricular pressures are equal should undergo coincident banding. This maneuver must precede the resection of the coarctation in order to avoid the acute exacerbation of left ventricular failure due to further volume overload. We disagree with Litwin et al.[10] that "prior aortic resection and anastomosis protects against the possible adverse effects of simultaneously embarrassing both ventricles." On the contrary, it has been our experience that volume overload of the already compromised left ventricle (with the initial resection of the coarctation) has proved consistently detrimental. Five patients in our recent series have had pulmonary arterial banding (Cases 3, 4, 6, 8 and 11, Table II). One (Case 4) died 12 hours postoperatively and was found to have corrected transposition of the great vessels with a complete A-V canal. A second patient (Case 8) died 1 month postoperatively from severe congestive heart failure. Postmortem examination of this patient demonstrated a secundum atrial septal defect, large ventricular septal defect and hypoplasia of the left ventricle. In one patient (Case 10) with a small interventricular gradient (20 mm Hg) a temporary band was placed before coarctectomy and immediately removed after resection.

There is currently enthusiasm for the primary repair of congenital heart defects utilizing deep hypothermia techniques, and total correction of a coarctation and ventricular septal defect may be carried out. Again, in the presence of a large shunt, temporary banding of the pulmonary artery should be performed before resection of the coarctation.

Indications for surgical resection: Nine children had less significant or no associated malformations. There were no postoperative deaths in this group. Consequently we believe that any child less than 1 year of age with coarctation of the aorta and associated left ventricular failure should have surgical resection. It has been our experience that although some infants manifest improvement in the first 24 to 48 hours of medical therapy, most become even more desperately ill or die suddenly before correction can be performed. Furthermore, persistent hypertension in the arms, multiple hospitalizations, failure to thrive and continued stress upon the left ventricle and arterial system have influenced this decision. We therefore initiate intensive digitalis and diuretic therapy, perform cardiac catheterization, and within 48 hours operate upon all infants with proved coarc-

tation who have presented with congestive heart failure.

Recoarctation: A most important criticism of coarctation resection in infancy is that anastomotic stenosis frequently redevelops.[12–14,16–18] The severity and time sequence for the development of this complication are quite variable. Factors involved in the recreation of the coarctation are probably multiple and include (1) inadequate anastomotic lumen, (2) thrombosis at the anastomotic site, (3) failure of the anastomosis to grow, and (4) retention of abnormal aortic tissues that provide progressive obstruction through the development of proliferative intima or hyperplastic media. Moderate stenosis (gradient between upper and lower limbs of 20 mm Hg or more) may not be associated with hypertension or left ventricular failure. Eight of 20 unselected patients previously reported on were in this category and were followed up.[17] Four additional patients had significant hypertension of the upper limbs and required reoperation. Twelve patients (60 percent) in the earlier series therefore demonstrated some degree of anastomotic stenosis. Simple and safe techniques for the resection of a recurrent coarctation have been developed and the relief of hypertension or pressure gradients between the arms and legs may be reduced or abolished.[11]

In the recent group, 5 of 15 children (33 percent) followed up an average of 20.6 months have significant blood pressure gradients. Only one child (Case 2) has severe hypertension. She weighed 1,100 g at the time of resection and showed evidence of recurrent coarctation 2 weeks postoperatively. This patient has been followed up for 22 months and is doing well on medical therapy. The four other children have gradients greater than 20 mm Hg, but none is severely hypertensive. The reduction in the incidence of recoarctation may be attributed to modifications in surgical technique. All involved tissue must be removed and the approximated lumens should be of near equal caliber. This often requires that the proximal portion of the left subclavian artery be utilized in the creation of a proximal lumen. The suture material used should be fine, that is 7-0 or 8-0 in size, and placed in interrupted fashion through the entire anastomosis.

Postoperative management: Since many of these patients have profound heart failure preoperatively we have been most attentive to ventilatory support in the postoperative period. Arterial blood gases are monitored closely and, with the development of pulmonary edema, atelectasis or pneumonia, arterial oxygen saturation may be maintained with the use of controlled positive airway pressure. Antibiotic therapy and frequent suctioning are utilized to control pneumonic infiltrates, and endotracheal tubes are often left for 24 to 72 hours. Aggressive digitalis and diuretic therapy is continued as preoperatively.

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Cardiac Catheterization in Small Infants: The Percutaneous Approach

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Cardiac catheterization of small infants can be performed by the percutaneous technique using materials readily available from commercial sources. Twenty infants averaging 3.0 kg (range 1.3 to 4.1 kg) underwent percutaneous sheath cardiac catheterization in a 12 month period. After refinement of the technique, cardiac catheterization in all small infants was attempted percutaneously with a 90 percent rate of success. This percutaneous approach has distinct advantages for the small infant because it is performed rapidly, preserves venous integrity and has a low rate of morbidity.

The advantages of percutaneous sheath cardiac catheterization in children are well known. Generally, the technique is quickly performed, preserves vascular integrity, minimizes formation of scar tissue, allows rapid exchange of catheters, reduces the threat of infection from a cut-down procedure and is readily acceptable to the patient and his parents. However, percutaneous sheath cardiac catheterization has not been widely used in small infants. Of 126 cardiac catheterizations performed in infants under 5 kg, only 4 were successfully done by the percutaneous technique in one large series.[1] This report describes the performance of cardiac catheterization by percutaneous sheath technique in 20 infants weighing less than 4.2 kg during a 12 month period. The materials used were readily available from commercial sources.

Materials and Methods

The technique of percutaneous sheath cardiac catheterization has been well described.[1–3] In small infants, a no. 5F percutaneous Teflon® sheath and dilator unit (U. S. Catheter and Instrument Corp.) is used. The femoral vein is entered with a 21 gauge, thin-wall, short bevel, scalp vein needle (Abbott Laboratories) from which the plastic tubing has been cut (Fig. 1). After a brisk flow of venous blood, a 0.045 cm (0.018 inch) diameter guide wire is advanced cautiously. Frequently, little to no resistance is met if the needle has entered the vein at a 45° to 60° angle and the guide wire can be manipulated above the diaphragm. If resistance to the wire insertion is met, slight withdrawal and more horizontal angulation of the needle may allow advancement of the guide wire. It is important to withdraw the tip of the wire into the needle lumen while manipulating the needle; otherwise, the guide wire tip may remain in an undesirable position along the vein wall and will be little affected by manipulation of the needle. Once the guide wire has been advanced above the diaphragm, the needle is removed and a 2 to 3 mm incision is made with a no. 11 blade to enlarge the puncture. After blunt dissection with a fine-pointed straight mosquito hemostat through the subcutaneous tissue, the plastic cannula from an 18 gauge Argyle Medicut® (Sherwood Medical Industries) is advanced over the guide wire into the subcutaneous tissue and femoral vein. The cannula is deeply advanced with approximately 1.0 cm of hub protruding above the skin surface to produce further dilatation of the

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subcutaneous tract and vein. After removal of the cannula, the no. 5 Teflon sheath and dilator can then be inserted in the vein over the guide wire with no difficulty. At the end of the cardiac catheterization, the sheath and catheter are removed and a pressure dressing is applied after hemostasis is achieved with finger pressure.

Results

Success rate: From December 1973 to April 1974, four of eight percutaneous attempts in small infants were successful. In the following months through November 1974, all cardiac catheterizations in small infants were attempted by the percutaneous technique, which was successful in 16 of 18 infants (89 percent). In most infants, the time for percutaneous insertion required less than 3 minutes. The average weight of the 20 infants in whom the percutaneous technique was used successfully was 3.0 kg (range 1.3 to 4.1 kg) (Fig. 2). After the technique was refined, failures occurred in two infants weighing 2.6 and 3.4 kg, respectively. No ready explanation for the failures was apparent; the catheterizations proceeded uneventfully by cut-down technique.

In very small infants the thinner arterial sheath of polypropylene (no. 5F) is recommended. This sheath was used in the smallest infant (1.3 kg) and there was no discernible cyanosis or edema of the leg 4 hours after the procedure.

Variety of clinical cases: Patients with a wide range of congenital heart diseases are represented in this report. There were three infants with critical pulmonary valve stenosis, three with tricuspid atresia, two with endocardial cushion defect, two with single ventricle and two with hypoplastic left heart syndrome. The remaining diagnoses included simple ventricular septal defect, atrial septal defect, mild pulmonary valve stenosis, double outlet right ventricle without pulmonary stenosis, coarctation of the aorta, peripheral pulmonary arterial stenosis and patent ductus arteriosus. One infant with normal findings was suspected to have had thrombosis of the inferior vena cava. No infants with simple transposition of the great arteries were encountered. When that diagnosis is made, balloon atrioseptostomy can be performed through a no. 7 sheath[4] after progressive venous dilatation.

Left heart catheterization: Since left heart entry with a venous catheter is usually possible in the infant, arterial catheterization is not usually required. Occasionally the left heart catheterization cannot be accomplished by the venous catheter and, in some infants, selective aortograms are essential. The percu-

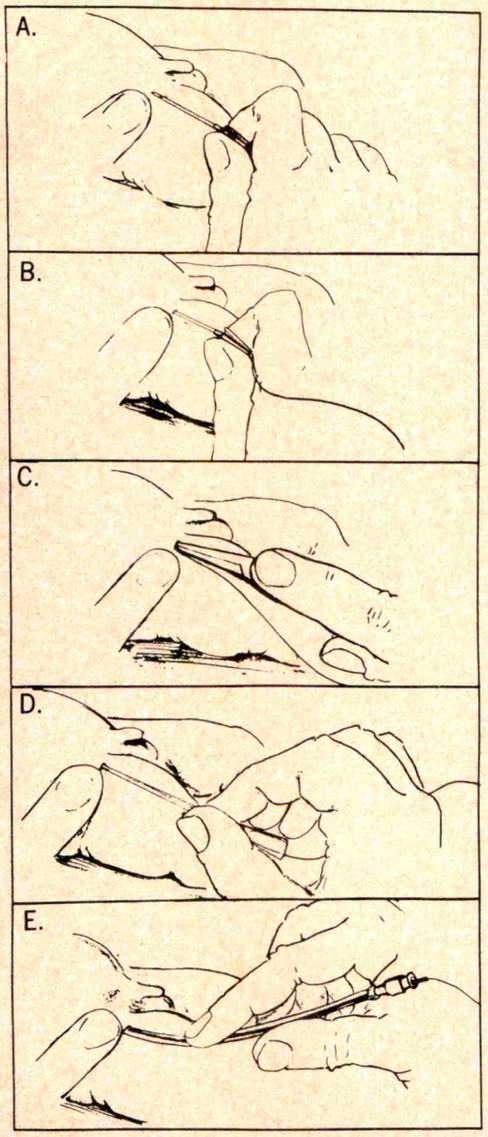

FIGURE 1. Percutaneous sheath cardiac catheterization in small infants. **A,** the scalp vein needle is grasped with the wings of the needle apposed. The operator's left index finger uses the right femoral artery as a landmark. **B,** after the 0.018 inch guide wire is advanced, the needle is removed while the left index finger immobilizes the guide wire by pressure over the vein. **C,** a straight hemostat creates a subcutaneous tract to the vein after the puncture is widened to 2 to 3 mm by no. 11 blade. **D,** a plastic cannula is advanced over the guide wire, dilates the subcutaneous tract and vein, then removed. **E,** the sheath and dilator unit is advanced over the guide wire into the vein. The dilator is withdrawn, and the catheter is then inserted into the sheath.

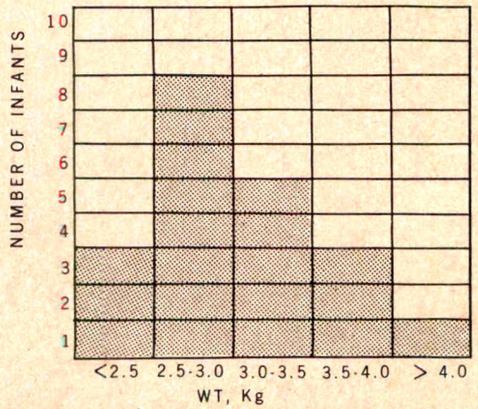

FIGURE 2. Weight distributions in infants undergoing percutaneous sheath cardiac catheterization.

taneous arterial catheterization is identical to venous cannulation but the thinner arterial sheath of polypropylene is used. Two infants not included in this series underwent percutaneous femoral arterial cannulation for aortograms in the evaluation of aortic arch anomalies. There was no morbidity associated with this procedure; arterial pulsations were intact after the catheterization.

Morbidity: Four infants had some cyanosis and mild swelling of the leg for 6 to 24 hours after catheterization without signs of arterial occlusion. No unusual bleeding occurred from the puncture site. Slight ecchymoses were observed occasionally. No large hematomas or infections were encountered.

Discussion

The technique of percutaneous sheath cardiac catheterization is applicable to the small infant. It is suggested that previously reported failures[1] were attributable to the use of relatively large needles and guide wires in the small femoral vein of the infants. Fortunately, miniature equipment for the successful application of the percutaneous technique to small infants is readily available in the form of the 21 gauge scalp vein needle and the 0.045 cm (0.018 inch) diameter guide wire. The routine use of a plastic cannula from an 18 gauge Argyle Medicut® to dilate the subcutaneous tract and vein has greatly facilitated the introduction of the sheath and dilator unit over the delicate 0.045 cm diameter guide wire. Kinking of the guide wire with difficulty in advancement of the sheath and dilator has not been a problem. The entire technique is easily taught and readily learned by physicians in training. Two physicians with less than 1 year's experience in the cardiac catheterization laboratory have successfully performed the catheterization in some of these infants.

Advantage over cut-down procedure: In our experience, cardiac catheterization with the cut-down technique may often be difficult in small infants because of the small caliber of the veins. These small veins may accommodate only small catheters (such as no. 4F) that have poor angiographic capability. Femoral venotomy, on the other hand, sometimes requires ligation of the vein at the close of the procedure. Without the indwelling sheath, the femoral vein may be severely traumatized with exchange of catheters and by the motion of the catheters within the vein. Signs of venous stasis for days after a cut-down procedure are not uncommon. Frequently, subsequent procedures cannot be performed on the side of a cut-down procedure because of femoral vein occlusion. In contrast, the percutaneous technique is rarely difficult or lengthy in small infants and appears to preserve femoral venous integrity in a large percentage of them. A no. 5F catheter can be used routinely with good angiographic results. Neither the size of the infant nor the severity of the cardiovascular lesion limits the success of the percutaneous technique.

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Ischemic Heart Disease: An Overview

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The studies on natural history of ischemic heart disease are reviewed and the major predictors of mortality identified. The severity of the coronary atherosclerosis and the status of ventricular function are found to be more important predictors of survival than the clinical presentation. The objectives of therapy in patients with ischemic heart disease are (1) to improve the quality of life by reducing symptoms, (2) to improve ventricular function, and (3) to increase survival time. The results of surgical therapy are examined in relation to these three objectives.

Symptomatic improvement is present in 85 to 95 percent of patients after surgery, but convincing evidence for improved ventricular function is lacking and controlled studies of natural history have failed to show that surgery increases survival time. Analysis of the mechanism of symptomatic improvement after surgery suggests that increased blood flow to the ischemic area as well as infarction of ischemic myocardium and the nonspecific effects of surgery may account for the improvement. The prevention of coronary atherosclerosis is viewed as an attainable long-term solution to the problem of ischemic heart disease.

A mass of information has been collected on the natural history of ischemic heart disease. In this paper I will review these data with special attention to stable angina pectoris and the objectives of therapy. An evaluation of surgical treatment will follow and the paper will conclude by presenting the case for prevention.

Natural History

The experience of the last 5 years has shown that certain factors are important in determining the prognosis of patients with ischemic heart disease and that others are unimportant (Table I). The clinical evidence that follows supports these findings.

Severity of Coronary Atherosclerosis

A life table plot of survival curves of patients with angina pectoris classified according to the severity of coronary artery disease is shown in Figure 1.[1] The scoring system is a simple one, with the higher scores assigned to patients with more severe disease. The data, from a study initially reported in 1970,[2] have been confirmed by several investigations summarized by Reeves[3] in his review of this subject.

Figure 2, taken from the recent study on natural history by Burggraf and Parker,[4] once again shows survival as a function of the severity of the coronary disease. In this study patients are classified according to the number of vessels involved. The difference between

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TABLE I

Natural History of Stable Angina Pectoris

Determinants of Prognosis	Not Determinants of Prognosis
1. Severity of coronary artery disease	1. Clinical presentation Severity of angina Rest vs. exertional angina
2. Ventricular damage Congestive heart failure Abnormal electrocardiogram Abnormal segment motion Abnormal hemodynamics	2. History of previous myocardial infarction

double and triple vessel disease apparent in the early years is absent after 5 years. However, the patients with single vessel disease are significantly better off than patients in the other two groups. Examination of the data from which this graph is derived indicates that the mortality rate is greatest in the 1st year for the group with single vessel disease. In the first 5 years there were seven deaths in this group of 101 patients, five in the 1st year, one in the 4th and one in the 5th year. This relatively good prognosis of patients with single vessel disease has been apparent from several other studies.[5]

The information on severity of coronary disease and survival can be summarized as follows: The mortality rate for two or three vessel disease is 10 percent a year, or about 50 percent in 5 years; that for single vessel disease is probably no more than 2 percent a year, or less than 10 percent in 5 years. This excellent prognosis applies to patients in the stable phase of their disease and cannot be applied to patients at the moment of occlusion.

Ventricular Function

The state of ventricular function is the second major determinant of prognosis. One of the earliest and simplest demonstrations of this important relation is to be found in Oberman's study (Table II). The population consisted of 85 patients, all of whom had two or three vessel disease; and the overall or total mortality for this group was 32 percent. Heart size was also measured on a standard chest roentgenogram, and the patients were classified in accord with this measurement. Comparison of patients with a heart size greater or less than 396 cc/m^2 reveals a more than threefold difference in the mortality rates of these two groups: 40 percent for patients with a large heart and 12.5 percent for those with a small heart.

As in the case of data on the severity of disease I will once again skip from old data to recent data and not mention many confirmatory studies reported in the interval. The most recent information on the relation between ventricular function and survival is to be found in the paper of Burggraf and Parker.[4] Figure 3, taken from that paper, shows that patients with normal hemodynamic states and normal ventriculograms have a far better prognosis than do those with abnormal hemodynamic states and abnormal ventriculograms.

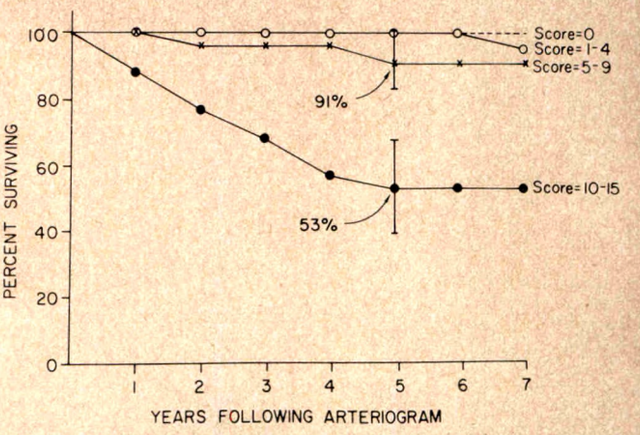

FIGURE 1. Survival of patients with angina pectoris as a function of the severity of the coronary atherosclerosis as determined by arteriography. The higher scores indicate more severe disease. Reproduced from Humphries et al.[1] by permission of the American Heart Association, Inc.

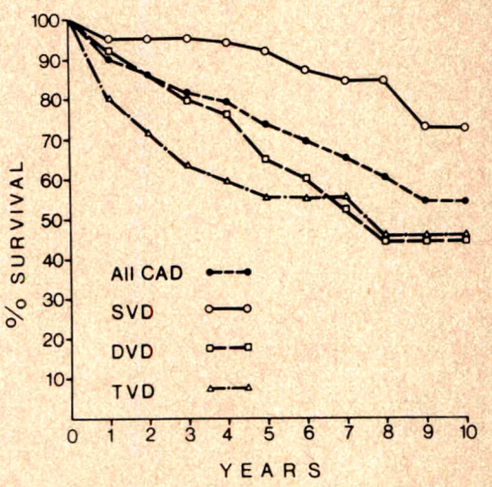

FIGURE 2. Survival of patients with coronary atherosclerosis as a function of the number of vessels involved. All CAD = entire group of patients with coronary artery disease; DVD = patients with double vessel disease; SVD = patients with single vessel disease; TVD = patients with triple vessel disease. Reproduced from Burggraf et al.[4] by permission of the American Heart Association, Inc.

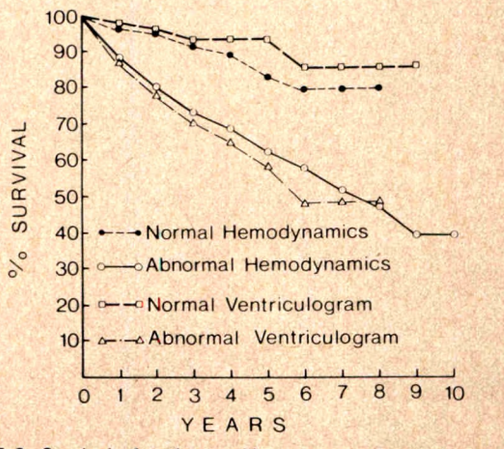

FIGURE 3. Survival of patients with coronary atherosclerosis as a function of the degree of ventricular dysfunction. Reproduced from Burggraf et al.[4] by permission of the American Heart Association, Inc.

TABLE II

Mortality Data at 50 Months in 85 Patients*

Diseased Vessels	Total Patients		Heart Size (cc/m²) ⩾ 396		<396	
	Dead	Alive	Dead	Alive	Dead	Alive
2	12	30	11	16	1	14
3	15	28	13	21	2	7
Total	27 (32%)	58	24 (40%)	37	3 (12.5%)	21

Adapted from Oberman et al.[5]

TABLE III

Ischemic Heart Disease: Objectives of Therapy

1. Relieve symptoms, improve quality of life
2. Improve ventricular function
3. Improve life expectancy
4. Prevent myocardial infarction

Other Factors

Strong evidence supports the severity of coronary disease and ventricular function as the two major determinants of prognosis in coronary artery disease (Table I). The magnitude of ventricular damage or the state of ventricular function may be measured as hemodynamic change, heart size, abnormalities on ventriculography, congestive heart failure or abnormal electrocardiogram; but these are all manifestations of the same condition. Table I, column 2, lists the factors that are not determinants of prognosis; that is, they are not primary determinants of prognosis independent of the severity of coronary disease and the degree of ventricular damage. Thus, patients with angina pectoris at rest are more likely to have severe coronary disease than those with angina only on exertion and patients with a history of a previous myocardial infarction are more likely to have ventricular damage than those who do not have such a history, but angina at rest or a previous infarction has not been shown to be a determinant of prognosis independent of the effect of the severity of coronary disease and the degree of impairment of ventricular function. An additional clinical factor that may be important in prognosis is an increase in the severity of symptoms. My former collaborator Friesinger believes that such a change in clinical status is an important factor with independent predictive value.[6]

The discussion to this point can be summarized by saying that the prognosis of a patient with ischemic heart disease can be determined by knowledge of the severity of the coronary disease and the degree of impairment of the ventricular function.

Objectives of Therapy

The objectives of therapy in ischemic heart disease are listed in Table III, and these will be used to analyze the results of surgical treatment. A similar analysis of the effects of medical treatment in relation to these objectives would be of interest but is not within the scope of this presentation.

Symptomatic Improvement

There is no question about the relief of symptoms that follows bypass graft surgery. In 80 to 90 percent of the patients the symptom of angina pectoris, be it stable or unstable, is diminished after surgery; and at least 60 percent of patients are completely asymptomatic. The improvement in symptoms is spectacular. "Improved quality of life" is important and a worthy objective of any therapeutic procedure. The

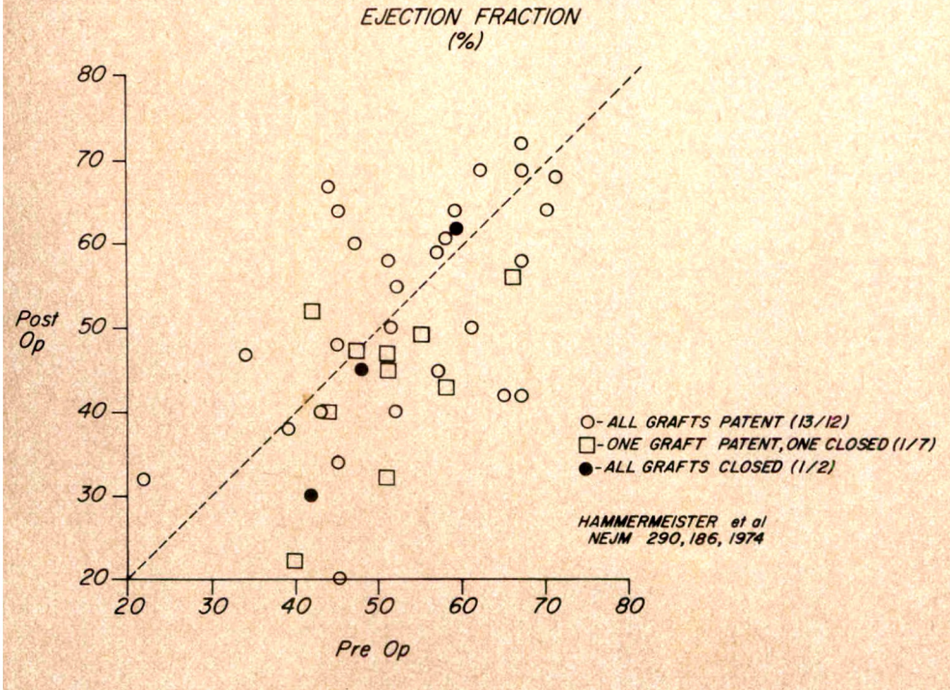

FIGURE 4. Change in ventricular function measured as ejection fraction following bypass surgery. Modified from data of Hammermeister et al.[8]

presence of disabling symptoms usually constitutes the prime indication for surgery, and it is clear that angina is relieved in the vast majority of cases.

Improved Ventricular Function

The second objective of therapy is to improve ventricular function, especially in situations in which it is impaired. One would not expect improvement in ventricular function if ventricular function were normal. There have been reports of improved function as assessed by ventriculography after vein bypass surgery in patients with acute myocardial ischemia.[7] It is possible that in these cases ventricular function was depressed to a subnormal level by ischemia and that revascularization restored it to a normal level.

Ventricular function has been measured in large groups of patients undergoing bypass surgery, and the data from Hammermeister et al.[8,9] are replotted in Figure 4. It is clear that there is no significant departure from the line of identity in this plot of ejection fraction before and after surgery. Similar data have been obtained by Scholer et al.[10] and by several other groups. To summarize the findings, ventricular function after bypass surgery shows no change in about 60 percent of patients, is worse in 20 percent and shows some improvement in 20 percent. It is possible that greater improvement may be found in certain special groups, such as patients with unstable angina, but this has not yet been firmly established.

Improved Life Expectancy

Prospective randomized studies: The third major objective is the improvement of life expectancy, and this is the most difficult to evaluate. Ideally, evaluation should be approached by a randomized prospective study, and several such studies are under way. Two possible designs are shown in Figure 5. These diagrams apply to studies of the effect of surgical therapy on unstable angina pectoris.[11,12] Similar designs can be applied to stable angina and, indeed, are used in the studies currently in progress.[13,14] The beauty of the prospective randomized study is that variations in prognosis attributable to variations in the severity of the arterial disease and in the state of ventricular function are eliminated by the random assignment of patients to the two treatment groups. Another advantage is that only those patients who are suitable for surgery are considered. Without randomization it is always possible that the patients with better ventricular function, and therefore a better natural history, will be selected for surgery and patients with poorer ventricular function, and hence a poorer prognosis, will remain in the group not operated on. Consideration of the data in Table II shows how great this effect might be and indicates that studies in which patients are neither chosen at random nor matched cannot be used to obtain meaningful data about the effect of surgery on natural history.[15]

Retrospective matched studies: The alternative to prospective randomization is retrospective matching of patients; this approach has been taken by the investigators at the Duke University Medical Center.[16] They studied a group of 402 patients treated medically and a group of 379 treated surgically. Allocation to these two groups was made not prospectively in accordance with a random design but in accordance with existing medical practice in that institution. The patients were characterized according to 89 different variables, and thus a match between the two groups based upon these 89 characteristics was possible retrospectively. This is the "next best thing" to a prospective randomized study. The important determinants of prognosis were described in detail with the severity of arterial disease being defined by 11 descriptors and ventricular function by 7.

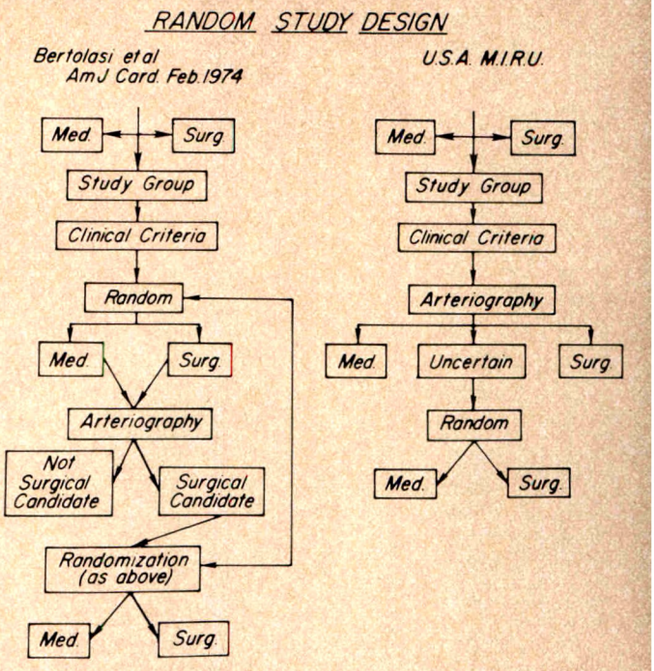

FIGURE 5. Diagrams of study design in two random prospective studies of unstable angina pectoris. The designs differ with respect to when in the sequence randomization takes place. Med. = medical; MIRU = Myocardial Infarction Research Units; Surg. = surgical. Data from Bertolasi et al.[12] and Conti et al.[11]

The similarity between the medically and surgically treated groups is remarkable and is one of the most interesting results of this study. The two groups differed with respect to severity of pain and prior treatment. Thus, the surgically treated group had more frequent attacks of pain, and the pain was more severe and disabling. Treatment with beta adrenergic blocking agents, nitroglycerin and long-acting nitrates was also more common in the surgically treated group. The two groups differed significantly with respect to several measures of ventricular function. The heart size was smaller and the ejection fraction higher in the surgically treated group. The two groups did not differ significantly with respect to the severity of coronary artery disease as determined by arteriography. These data indicate that actual practice at the Duke Medical Center tended to select for

surgery patients with severe symptoms and good left ventricular function. Thus the surgical cohort would have a better prognosis irrespective of the form of therapy by virtue of the larger number of patients with good ventricular function in this group. The existence of this natural and not unexpected bias casts doubt on the conclusions of any study dealing with the effect of surgery on life expectancy in which patients are not selected at random or at least matched with respect to factors determining prognosis, especially ventricular function.[15]

Survival data for the medically and surgically treated populations is shown in Figure 6A, and there is no difference in survival at 2 years. It appears that survival in the surgically treated group stabilizes at 2 years, but the natural history studies shown in Figures 1 and 2 indicate that the untreated or medically treated population may also be characterized by survival curves of lesser slope after the 3rd or 4th year.

A similar survival curve for a low risk subset of the total population is shown in Figure 6B. These patients fall into two categories with respect to the important determinants of prognosis: (1) two to three vessel disease with normal ventricular function, and (2) one vessel disease with abnormal function. In this group it is obvious that the prognosis without surgery is exceedingly good and at 2 years survival is greatest in the group treated medically. McNeer et al.[16] also analyzed a group of patients with a high risk and in one small subset has evidence suggesting that this group might be better with surgical therapy, but the results are not conclusive.

TABLE IV

Results of Bypass Surgery, 1975

	Percent of Patients
Symptomatic improvement	85
Improved ventricular function	20
Increased survival time	??

The retrospective study with matched cases carried out at Duke has failed to show any clear-cut improvement of surgical therapy over medical therapy at 2 years. It is possible that in certain subsets of low risk patients medical therapy may be preferable to surgical, and in other populations surgical therapy may be preferable to medical therapy. The results from this well performed retrospective study are confirmed by the preliminary results from at least three ongoing prospective randomized studies.[13,14,17]

Thus, in summary, the results of prospective randomized studies and retrospective matched studies fail to demonstrate increased survival after surgical therapy in patients with stable angina pectoris.

Mechanisms of Improvement

Table IV summarizes the current situation. Symptomatic improvement is present in 85 percent of patients, but ventricular function is improved in only 20 percent of patients at the most, and there is no convincing evidence that survival is altered. Careful consideration of these findings reveals an inconsistency and stimulates the question: If symptomatic improvement is attributable to improvement in the cor-

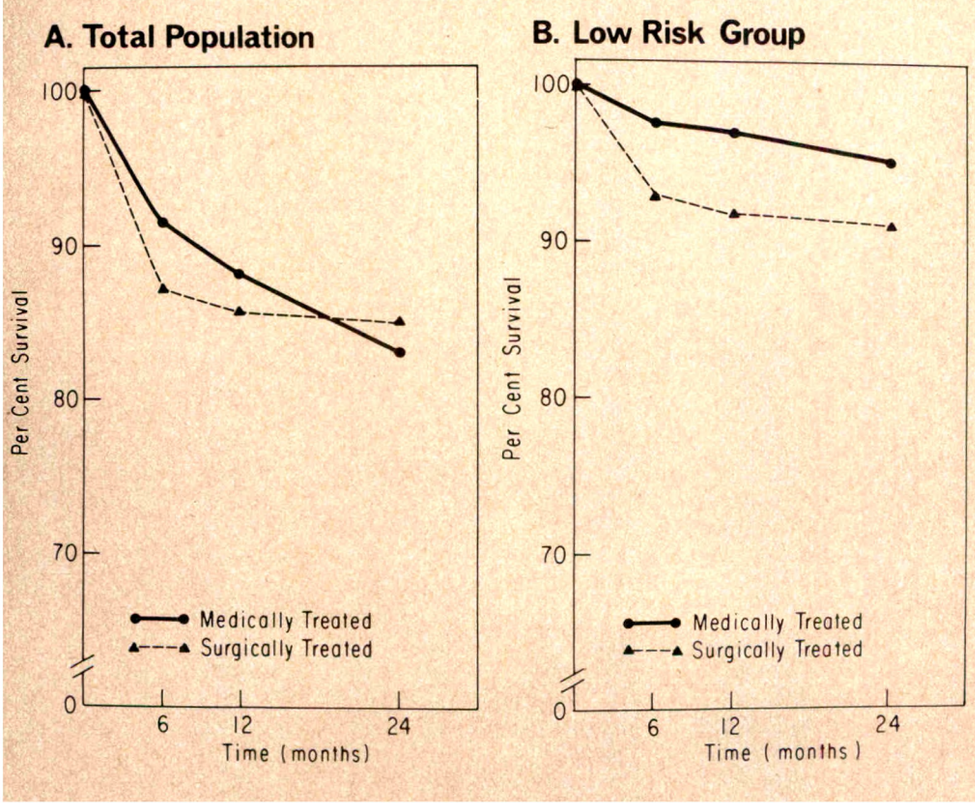

FIGURE 6. Survival of medically and surgically treated groups. **A,** total population. **B,** low risk group. Reproduced from McNeer et al.[16] by permission of the American Heart Association, Inc.

TABLE V

Fallacious Logic in Interpreting Results of Bypass Surgery

1. Coronary atherosclerosis causes myocardial ischemia
2. Myocardial ischemia causes
   a. Angina pectoris
   b. Reduced life expectancy
3. Vein bypass graft relieves angina pectoris
   (assumption: angina relieved because ischemia relieved)
4. Therefore: vein bypass graft improves life expectancy

onary circulation, why is it not possible to demonstrate improvement in survival?

This discrepancy is highlighted by consideration of the treatment of pneumococcal lobar pneumonia by penicillin. In this disease a favorable change in symptoms is associated with a favorable change in objective evidence of disease and prognosis. Penicillin makes the patient feel better, the fever disappears, the chest X-ray film shows resolution, and the patient is more likely to survive. This uniform response of all the manifestations of disease occurs because the therapy (penicillin) acts specifically on the primary disease process (pneumococcal infection). Statistics are not necessary to demonstrate the effect of penicillin in pneumococcal pneumonia. It is clear to the patient and to his doctor that all aspects of his disease are improved by the therapy and, indeed, the mortality statistics and objective measurements are merely confirmatory.

The situation is far less clear in the case of bypass surgery for coronary artery disease. The discrepancy between the changes in symptoms and the change in prognosis suggests that the therapy may not have a specific effect on the disease process in all cases. Enthusiasts for bypass surgery often make statements such as the following: "It is perfectly obvious that the dramatic improvement in symptoms that follows the operation must mean that the patient's disease state is alleviated."

At this point let us consider other things that are "perfectly obvious." I refer specifically to optical illusions (Fig. 7). If two bars of equal length are laid on a photograph of a railroad track, the bar farthest from the observer will appear to be longer. It is "perfectly obvious" to the observer that the more distant bar is longer, but measurement will show that the two are the same size. Sometimes things that are "perfectly obvious" turn out to be true as in the case of penicillin and lobar pneumonia, but in other situations measurements do not support differences that appear to be "obvious."

Table V presents in another form the fallacious logic responsible for some of the problems in interpreting results of vein bypass surgery. There can be no disagreement with the statement that coronary atherosclerosis causes myocardial ischemia. It is likewise established that myocardial ischemia causes both angina pectoris and reduced life expectancy. The third statement, that vein bypass graft relieves angina pectoris, is also true in 85 percent of cases. At

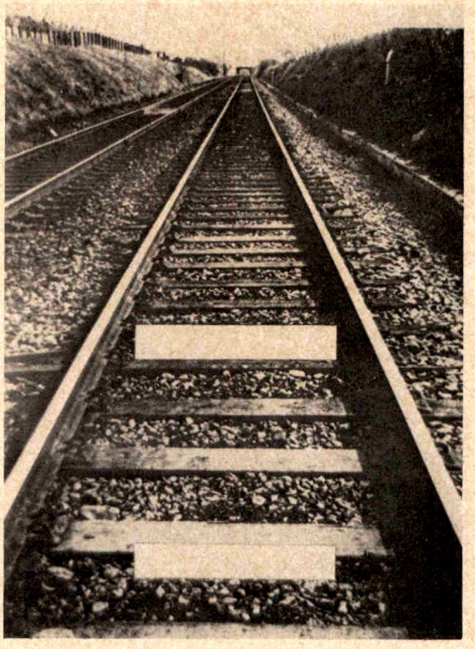

FIGURE 7. An optical illusion. The two white bars are the same size.

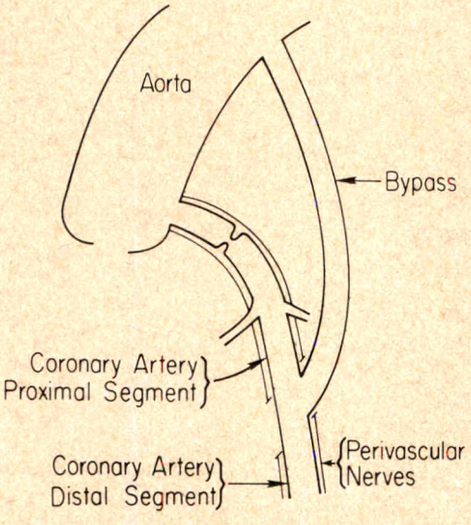

FIGURE 8. Diagram of bypass procedure illustrating possible mechanisms of symptomatic improvement.

this point, an assumption is often made and not recognized as an assumption, namely, that angina is relieved because ischemia is relieved. The final statement, therefore—vein bypass graft improves life expectancy—is based upon an assumption. Unfortunately, therapeutic decisions are often based upon a sequence of faulty logic containing an assumption that must be questioned. If some mechanism other than increased blood flow accounts for the relief of angina it is not logical to assume that life expectancy will be improved.

Alternative Explanations of Improvement

Production of myocardial infarction: Mechanisms of improvement other than increased blood

flow can be considered with the aid of the diagram in Figure 8, which depicts the aorta and a diseased coronary artery with a single proximal stenotic lesion. A bypass has been created between the aorta and the coronary artery distal to the obstructing lesion. Under ideal circumstances the graft and the artery remain patent and, therefore, an alternative route is provided whereby blood can reach the distal coronary artery. Unfortunately, in a significant number of cases the ideal situation does not exist. First, let us consider the changes that may occur in the patient's coronary artery, which has been referred to as the native or intrinsic coronary circulation.[18,19] When the bypass is working well most of the blood flow to the distal artery goes through the bypass, and flow through the proximal segment containing the stenotic lesion becomes sluggish and thrombosis frequently occurs. This may be of no significance if the bypass remains patent, which it does in approximately 70 percent of cases; but it becomes occluded in 30 percent.[20] If a segment of the artery is occluded and the bypass is occluded, the blood supply to the distal myocardium will obviously be impaired and infarction may occur.

The occlusion of the proximal segment may be important even when the graft remains patent. The blood supply to vessels arising from the proximal portion of the coronary artery will be eliminated, and there will be an area of myocardial infarction.

Sometimes the distal coronary arterial segment becomes occluded. This is especially likely to occur if the graft is occluded, but it may occur even with a patent graft. In most instances this change can probably be attributed to the suturing of the bypass graft to a diseased coronary artery. The presence of disease in the distal coronary arterial tree which interferes with runoff is also important in this situation. Therefore, occlusion of either the proximal or distal coronary artery with or without occlusion of the graft can result in myocardial infarction; and this is a possible explanation for the relief of symptoms in some patients.[21,22]

Interruption of perivascular nerves: Another possible explanation is that the perivascular nerves accompanying the coronary artery are interrupted by the mobilization of the vessel and the placement of the graft.[23] Because too little is known about the pain pathways from the heart, this explanation can only be said to be theoretically possible.

It is becoming increasingly obvious that changes in the native or intrinsic circulation are not rare.[18,19,24–27] The results of a number of studies from four institutions are summarized in Table VI. The listed number of new total coronary occlusions includes both proximal and distal segment occlusions, and proximal segment obstructions are approximately five times more common than occlusions of distal segments. This table shows that occlusions are frequent even in the presence of patent grafts (39 percent), more common when the graft is occluded (47 percent) and considerably less frequent in the absence of a graft (6 percent). This last fact is of great importance since it has been suggested that the appearance of these new occlusions represents progression of the disease. Serial studies of vessels not grafted indicate that new occlusions appear with a frequency of only 6 percent with an average interval between studies of 6 months.

When the native or intrinsic circulation lesions were first described there was a widespread tendency to attribute them to surgical technique or angiographic artifacts. It is clear now that they are real phenomena and occur with significant frequency in a variety of institutions in the hands of a number of competent surgeons. It can be said that they have been found by everyone who has looked for them and those who deny their existence have failed to look. The superficial examination of a postoperative angiogram is not adequate to detect this change. The preoperative and postoperative films must be projected side by side and each vessel systematically examined in each film. If this systematic matching of the pre- and postoperative vascularity is carried out, the changes described will occur with the frequency indicated in Table VI.

Evaluation of mechanisms of postoperative symptomatic relief: The practical problem of find-

TABLE VI

Changes in Native Coronary Circulation After Bypass Surgery*

Bypass Graft	Coronary Arteries Examined (no.)	New Total Occlusions (%)
Patent	404	39
Occluded	184	47
None	423	6

Adapted from Griffith.[28]

TABLE VII

Results of Bypass Surgery for Ischemic Heart Disease, 1975

	Percent
1. Symptoms alleviated and exercise tolerance improved	80–90
2. Asymptomatic	60–70
3. Surgical mortality	
Good left ventricular function preoperatively	0–4
Poor left ventricular function preoperatively	20–40
4. Vein graft patency	70–80
5. Occlusion in native circulation (in presence of patent graft)	30
Proximal	25
Distal	5
6. Ventricular function	
Improved	20
Unchanged	60
Worse	20
7. Postoperative infarction (new Q wave)	10–25
8. Percent survival at 2 years (Duke study[16])	
Total (781 patients)	
With surgery	85
Without surgery	83
At low risk	
With surgery	92
Without surgery	95
At high risk (with or without surgery)	70

ing an explanation for symptomatic relief in a particular patient is illustrated in Figure 9. Four situations that may be encountered at the time of postoperative study are described. In situation A, bypass grafts 1 and 2 are patent. In this situation it is possible to attribute the improvement in symptoms to increased blood flow to one or both of these areas. This is the explanation that we hope accounts for the improvement, but even in this ideal case there are other possible explanations. The other end of the spectrum is depicted in situation D. This situation is fortunately becoming rare, but every center has a few such cases, and they provide information of great value in understanding the mechanism of improvement. In this situation both bypass grafts have closed and the two arteries to which they are connected are also occluded. It is impossible to say that the symptomatic improvement is attributable to increased flow because, if anything, there is decreased flow to both areas and infarction of previously viable myocardium has almost certainly occurred. Another explanation must be found for the symptomatic improvement in this patient.

It is possible that infarction of an ischemic and angina-producing area is responsible for the symptomatic relief. A second possibility is that the denervation of the ischemic area in responsible for the relief. A third possibility is the nonspecific effect of surgery so well described by the beautiful studies of Cobb et al.[29] and Dimond et al.[30] This has also been referred to as the placebo effect by Beecher[31] and Ross.[32] The placebo effect was also demonstrated by studies of the Beck procedure (pericardial poudrage) and the Vineberg procedure (internal mammary implant).[33] The possibility of coronary arterial occlusion and myocardial infarction cannot be excluded in these patients, and indeed new total occlusions have been found in patients restudied after a Vineberg procedure.[34]

Situation B in Figure 9 is of special interest. Bypass graft 1 to artery 1 is patent, but graft 2 and artery 2 have become occluded. Symptomatic relief could be due to increased flow to the distribution of artery 1 or to infarction in the distribution of artery 2, to the denervation of the painful area caused by the mobilization of the arteries, or to the nonspecific effects of surgery.

The interpretation of situation C is also a problem because here graft 1 to artery 1 is patent, and artery 1 is patent. Artery 2 was not the site of a graft, and indeed was not even manipulated at surgery, but at the time of restudy it is seen to be occluded. This is an example of the spontaneous closure that occurs in about 6 percent of nonbypassed arteries (Table VI). If at the time of the postoperative examination the native circulation is not carefully examined by side to side comparison with the preoperative study, the occlusion of artery 2 may not be noted. Therefore, on the basis of the usual postoperative examination, which is concerned primarily with the patency of the graft, the symptoms would be attributed to increased

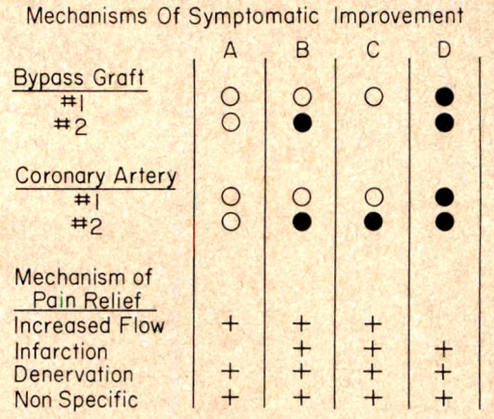

FIGURE 9. Mechanisms of symptomatic improvement after vein bypass surgery. **Open circles** = patent graft or coronary artery; **closed circles** = occluded graft or coronary artery; + = possible.

flow in the distribution of artery 1. This may be correct, but it is equally possible that the relief of symptoms is due to infarction in the distribution of artery 2, denervation of artery 1 or the nonspecific effects of surgery. Figure 9 could be expanded manyfold to include all the combinations that are possible and that have been encountered in actual practice.

Of additional value in the interpretation of postoperative studies are observations of the motion of segments of the ventricular wall perfused by the vessels to which grafts have been connected. Serial electrocardiographic studies are also useful in determining whether a segment of myocardium has been infarcted, and the location of the changes provides information about the location of the damage.[22] The absence of segment motion or the presence of electrocardiographic changes, or both, adds confirmatory evidence to the existence of an infarction.

Significance of postoperative myocardial infarction: It seems unlikely that postoperative infarction accounts for all the symptomatic improvement seen after surgery since dramatic relief of angina is seldom seen after spontaneous infarction. On the other hand, myocardial infarction after surgical manipulation of the vessel is quite different from infarction that occurs spontaneously. In the surgical situation a large trunk is totally occluded, and no filling of the distal vessel is seen at arteriography. The arteriographic pattern in patients who have sustained a spontaneous infarction differs in that there is usually collateralization and filling of the vascular bed distal to the obstruction. It is also clear from Figure 9 that the relief of pain could be attributed to denervation of the ischemic zone or to the nonspecific effects of surgery, and there is no way to be sure which mechanism is responsible. The message in Figure 9 is that the situation is complex and that increased blood flow to the ischemic area is not the only possible explanation for the symptomatic improvement.

It is possible that survival time might be increased even in patients who sustain a myocardial infarction. This possibility is based on the belief that a completed infarct with a healed scar is less likely than an

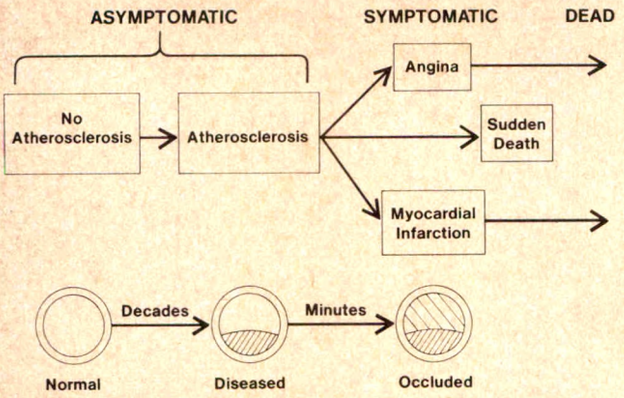

FIGURE 10. Pathogenic sequence leading to symptomatic coronary artery disease.

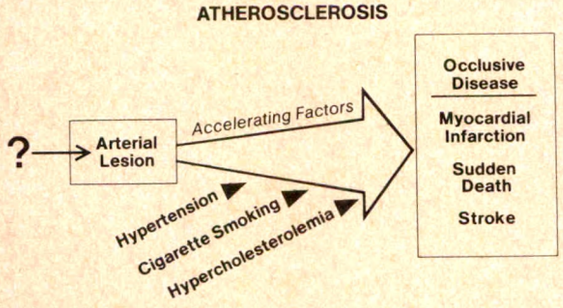

FIGURE 11. Approach to prevention of coronary atherosclerosis.

ischemic area to be the site of origin of potentially fatal arrhythmias. This presumption is consistent with the data of Cobb et al.[35] from the Seattle Heart Watch. They showed that patients surviving resuscitation for ventricular fibrillation could be classified into two groups: those who had a myocardial infarction, as evidenced by serum enzyme elevation and Q waves, and those who did not. The mortality rate in subsequent years was greater in the group who did not have an infarction. This observation suggests that the electrical instability is corrected by the defibrillating shock but that the unstable situation that leads to the fibrillation remains and the arrhythmia may recur in the patients who do not have an infarct. Those who have an infarction are better off because the unstable condition has been removed.[36]

Present Status of Coronary Bypass Surgery

The situation with regard to bypass surgery for ischemic heart disease in February 1975 is summarized in Table VII.

Mortality: The surgical mortality figures are worthy of comment and prove that a good cardiac surgeon can select any mortality figure he wishes by selecting his patients. If patients at good risk with good ventricular function are selected for surgery mortality figures of less than 1 percent can be obtained. On the other hand if a surgeon accepts patients with a low ejection fraction and akinetic segments the mortality figures will be higher. Variation in mortality is a function of the kind of patients selected for surgery as well as of surgical skill. It is also clear that patients with unstable angina, strictly defined as those with pain at rest and associated S-T segment changes, will have a higher operative mortality rate than patients with stable angina.

Postoperative infarction: The incidence rate of postoperative infarction, defined as the presence of new Q waves, has been estimated to be 10 to 25 percent and these estimates correspond relatively closely with the occurrence of changes in the native circulation in patient series in which these changes have been sought.[37] If the diagnosis of infarction is limited to patients who manifest a new Q wave the incidence of infarction will be underestimated.[22]

Symptomatic improvement: Coronary bypass surgery in 1975 is an excellent treatment for the symptoms of angina pectoris and will result in symptomatic improvement in 80 to 90 percent of patients; 60 percent will be totally asymptomatic. The available evidence will not support a general statement that the procedure decreases the likelihood of a subsequent myocardial infarction or improves life expectancy. It is possible that prognosis may be improved in certain subsets of patients, but this remains to be established.[16] Prophylactic surgery in asymptomatic patients cannot be justified by the facts available in 1975. There may be certain special situations such as proximal disease of the left main coronary artery in which the prognosis will be improved by surgery, but this has not yet been proved either by the retrospective study of matched patient series or by the prospective randomized studies.

The Case for Prevention

No overview of ischemic heart disease in 1975 would be complete without a strong plea for prevention.[38] If one examines the flow diagram of the disease process as displayed in Figure 10, it is clear that this entire paper has been concerned with the symptomatic patient who already has occlusive disease resulting in angina or myocardial infarction. The disease that has brought the patient to this point in his natural history began decades ago, and it should have been prevented by action taken throughout his life. By the time he has angina he has "end stage" disease, the vessels are severely narrowed and the myocardium is usually damaged.

When one examines a diseased coronary artery and notes the tortuous lumen, the friable walls, the calcification and ulceration it is clear that it may already be too late and that surgery may not provide the answer. I am reminded of the cardiac surgeon who was describing the aortic valve in calcific aortic stenosis and speculating on the possibility of surgical correction in the era before prosthetic valves were available. He said, ". . . even if you could take it out of the body and carry it over to the window and work on it in good light there would be nothing you could do with it." I think that this description could be applied to many of the coronary arteries in symptomatic patients. It indicates how difficult it is to approach the disease at this late stage and should strongly motivate us toward prevention.

Risk factors: Although we do not know everything about the cause of the arterial lesion in atherosclerosis, there is good evidence that the progress of the disease is accelerated by cigarette smoking, hypertension and an elevated serum cholesterol level (Fig. 11). There is also evidence that reduction in these risk factors brings about a reduction in the risk of disease. In the face of these facts there would appear to be no excuse for the medical profession to limit its attention to symptomatic patients with far advanced disease. These patients should not be ignored, but the physician also has a responsibility to presymptomatic persons in the community. There is no evidence as yet that bypass surgery can reduce the death toll from coronary disease, but I believe that preventive measures can. There has already been a downturn in heart disease mortality that can be attributed to the modification of the three major risk factors. There is an increasing body of data from primate studies showing that atheromatous lesions can be made to regress.[39] There are also preliminary studies showing regression of atheromatous lesions in man. We must continue to look for better ways to treat our symptomatic patients, but we must not delay further in our attempt to prevent the disease before irreversible damage has developed.

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Experiments on Heart Valves (1908) by Harvey Cushing and J. R. B. Branch

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Experiments on canine heart valves were performed repeatedly during the last quarter of the 19th century. The work had been undertaken for a variety of reasons. Most of the experimenters had attempted to study the physiologic and anatomic effects of artificial lesions. This purpose is seen in the experiments of Cohnheim (1877–80), Klebs (1875), Rosenbach (1878), François-Franck (1882), and Stricker (1883); the reports of all these workers have been described and discussed in this Journal.[1–6] In at least one instance[7] the experiments were conducted in part in order to supply material for classroom demonstrations in pathology and physiology. Another report[8] shows that the same kind of experiment was being used in the explanation of physical signs and in the teaching of physical diagnosis.

With the contribution by Cushing and Branch, excerpted here, there is evidence of a new phase. The possibility of a surgical attack on valvular disease in man is now envisioned clearly and discussed overtly in a purposeful manner. The valvular lesion that figures most prominently in the discussion is mitral stenosis.

At the time of these experiments Cushing, later one of the world's foremost neurosurgeons, was an associate in surgery at Johns Hopkins Hospital. Prominent among his activities was the teaching of experimental and operative surgery to undergraduate medical students. The work was conducted at the "Old Hunterian" laboratory. A detailed account of Cushing's development and achievements will be found in the biography by the late Dr. John Fulton.[9] Dr. Joseph R. B. Branch, a graduate of the Johns Hopkins Medical School, was later to gain distinction as a surgeon and gynecologist in China.

The following excerpts have been taken from a paper by Cushing and Branch that appeared in 1908.[10]

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Excerpts from Paper of Cushing and Branch

We wish to mention briefly some attempts which have been made in the Hunterian Laboratory to reproduce chronic valvular lesions; to record certain cases of spontaneous valvular disease in the dog which have come under our observation; and finally to comment on the possibilities of future surgical measures in man directed toward the alleviation particularly of the lesion characterizing mitral stenosis.

In November, 1905, there was brought to the laboratory a large Newfoundland dog suffering with general anasarca, ascites, and other sequelae of passive congestion due to tricuspid insufficiency with compensatory failure resulting from advanced chronic endocarditis. A report of this patient's case was made at the time by Dr. Henry,[11] who had assumed the responsibilities of his treatment . . . . Autopsy disclosed a thickened mitral valve, a dilated and hypertrophied heart showing tricuspid insufficiency, together with an unusually marked degree of venous congestion.

Being then unaware that bloody ascites could result from chronic passive congestion of cardiac origin, we undertook to reproduce this condition experimentally. It was necessary, for the success of the investigation, that the animals should survive a sufficient length of time for the late consequences of the valvular lesions to manifest themselves.

In this research we were greatly aided by the observations which at that time were being made by Dr. W. G. MacCallum in the Hunterian Laboratory[12] on the vascular disturbances resulting from acutely produced valvular lesions. The ingenious cutting hook or valvulotome which he had devised was utilized in many of our experiments.

So far as we know ours have been the first successful attempts to produce valvular lesions by an intrathoracic direct exposure of the heart with subsequent recoveries . . . .

For the production of insufficiency the apex of the heart is caught by fine sutures, between which the valvulotome is introduced into right or left ventricle; the particular leaflet, lesion of which is desired, is then divided by the cutting hook. This step of the operation requires much practice on the cadaver in order that the operator become familiarized not only with the anatomical situation of the parts, but with the peculiar sensation imparted to the hook on cutting through the valve or the chordae tendineae. Very little bleeding results from the procedure; in fact, less bleeding than when the approach is made to the heart by way of the

auricle, although the latter method has been used in certain cases for producing mitral or tricuspid lesions.

Stenoses have been produced by passing a stout ligature on a blunt-pointed, curved needle into the cavity of the heart at or below the level of the auriculoventricular ring. The ligature, which should be dipped in boiling vaseline to prevent its acting as a source of clotting (Carrol), must catch two of the leaflets or the chordae passing to them. It may then be tied sufficiently tight to narrow the lumen to the desired extent. Owing to its inaccessibility this is a particularly difficult operation in the case of the mitral valve and we have as yet been unsuccessful in having a recovery after an extensive mitral lesion of this sort.

The operations performed by Drs. Henry and Heuer were twenty-five in number; eight of the animals died from one cause or another during the course of the operation; six of them succumbed to infection; eleven recovered. In all instances of recovery, however, the heart was enabled to compensate rapidly for the lesion, and possibly it will be necessary for the operation to be done in successive stages in order to reproduce conditions of compensatory failure such as occur in chronic endocarditis resulting from disease, the extent of the lesion being increased each time. We have, in other words, been unable to produce at one sitting and without fatality a lesion serious enough to cause a relative tricuspid insufficiency with serious passive congestion . . . . Consequently the primary object of this research—namely, the production of bloody ascites in chronic passive congestion due to compensatory failure—has as yet not been rewarded with success. These animals, however, have been of considerable value for the class in physical diagnosis in the study of the cardiac murmurs due to known valvular lesions . . . .

It is only a few years since the surgery of the heart was practically unknown. The first steps taken were in the direction of simple paracentesis for pericardial effusions, a measure which soon led to open drainage in suppurative pericarditis—a bold undertaking fifteen years ago. Then, following the demonstration on dogs by Del Vecchio before the International Congress in Rome in 1894 and the reported observations by Rosenthal (1895) and Bode (1897), which showed that operations on the heart wall itself—at least in animals—were feasible, a number of successful cases of direct suture for stab wounds and the like were soon recorded.[13] (Coppelen, 1896, Farina, 1896, Rehn, 1897, Parrozzani, 1897, etc., up to 1904, when Ricketts collected fifty-six recorded cases.) Surgeons thus became aware, through animal experimentation, that the musculature of the pulsating organ could hold sutures and would tolerate a considerable degree of manipulation. Indeed, those who have not experimented with surgical measures on the heart of the lower animals can little realize how much handling, dislocation, ligation of coronary vessels and the like will be borne, and how readily an incised opening, even into the cavities, may be made and subsequently closed. It is not such a great step to pass from the treatment by suture of accidental wounds of the musculature to the actual entering of the heart in the effort to attack pathological lesions of the valves themselves . . . .

During the course of our observations our attention was called by Dr. [T.B.] Futcher to a recent note in the *Lancet* by Sir Lauder Brunton,[14] which puts the matter from a physician's point of view so forcibly that his words may well be used to express our own feeling in regard to these measures should it ever prove justifiable to transfer the experiment to man. He says:

"Mitral stenosis is not only one of the most distressing forms of cardiac disease, but in its severe form it resists all treatment by medicine. On looking at the contracted mitral orifice in a severe case of this disease one is impressed by the hopelessness of ever finding a remedy which will enable the auricle to drive the blood in a sufficient stream through the small mitral orifice, and the wish unconsciously arises that one could divide the constriction as easily during life as one can after death. The risk which such an operation would entail naturally makes one shrink from it, but in some cases it might be well worth while for the patients to balance the risk of a shortened life against the certainty of a prolonged period of existence which could hardly be called life, as the only conditions under which it could be continued might to them be worse than death.

"I was much impressed by the case of a man under middle age whom I had under my care at St. Bartholomew's Hospital. For no fault of his own, but simply because of his disease, this man was really exiled from his family and one might almost say imprisoned for life, inasmuch as he could only live in a hospital ward or a workhouse infirmary. Whenever he left the hospital or infirmary with an amelioration of his distressing symptoms and returned home the exertion brought on an exacerbation and he had to leave home again in a few days to return to the hospital or infirmary. It occurred to me that it was worth while for such a patient to run a risk, and even a very grave risk, in order to obtain such improvement as might enable him at least to stay at home. But no one would be justified in attempting such a dangerous operation as dividing a mitral stenosis on a fellow-creature without having first tested its practicability and perfected its technic by previous trials on animals."

Thus we are really acting upon a suggestion originally made by Sir Lauder Brunton. We, however, have carried his efforts to the living animal; we have improved upon the method of entering the chest, and we have succeeded in obtaining operative recoveries after considerable number and variety of experimental valvular lesions made by a direct approach to the valve through the heart wall. It remains to demonstrate the possibility that an experimentally produced mitral stenosis with compensatory failure can be symptomatically improved by division of the narrowed mitral orifice on the living animal, before attempting, by a similar procedure, to relieve the corresponding pathological lesion in man.

Comment on Paper by Cushing and Branch

The investigation described was triggered by the discovery of hemorrhagic ascites in a Newfoundland dog. The lesion proved to be part of the syndrome of chronic passive congestion caused by disease of the mitral and tricuspid valves. The experiments began with an effort to reproduce the congestion and the bloody effusion.

In some of their series Cushing and Branch followed the work of MacCallum[7,8] and used his valvulotome, which was inserted into the heart by way of the great vessels. Cushing and Branch, however, preferred to use direct transthoracic exposure of the heart, the instrument being passed through the myocardium. Positive pressure was applied to the lungs through a tracheotomy. The intention was to procure long-term survival of the animals and to observe long-term effects.

In the creation of valvular insufficiency the instrument was inserted through the wall of the ventricle and a valve leaflet was cut; this procedure required much practice. Attempts were also made to produce stenosis by passing ligatures in the region of the atrioventricular ring. These trials were much less successful; in the case of the mitral valve no recoveries were obtained.

Toward the end of their essay Cushing and Branch summarize the history of cardiac surgery. The whole story covered no more than 15 years.

The experimenters record also the famous suggestion of Sir Lauder Brunton, which had been brought to their attention by Dr. T. B. Futcher. Brunton's comment doubtless had an inspiring influence on many progressive physicians.

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Coronary Insufficiency in Children

Coronary Arteriographic Studies in Two Siblings from a Family with Hyperbetalipoproteinemia

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A family affected with hyperbetalipoproteinemia was studied. Two siblings, a boy 11 and a girl 9 years of age, with characteristic findings of homozygous type II hyperlipoproteinemia are described. The highly atherogenetic nature of this disorder is illustrated by the occurrence of progressive coronary atheromatosis in the boy, in whom two coronary arteriographic studies documented the development of progressive obstruction of two coronary arteries in the course of 2 years. During this interval angina pectoris developed followed by myocardial infarction, cardiomegaly and congestive heart failure. The sister has remained asymptomatic, with apparently normal coronary arteries at age 9 years. Phonocardiograms were suggestive of aortic valve involvement although no aortic valve gradient was demonstrated by cardiac catheterization.

Familial type II hyperlipoproteinemia is a well known cause of premature and accelerated ischemic heart disease due to coronary atherosclerosis.[1–4] Recently we studied two children of a family affected with this abnormality. The progressive nature of coronary atheromatosis was observed directly by means of coronary cinearteriographic studies performed within a period of 26 months; during the course of this period total occlusion of two coronary arteries developed in one of the patients. These findings and related studies in other members of the family form the basis of this report.

Clinical Studies

Lipid Analyses

Total serum cholesterol was determined by the method of Abell et al.[5] and serum triglycerides by the procedure of Van Handel and Zilversmit[6]; lipoprotein electrophoresis was carried out on paper according to the method of Lees and Hatch.[7] Table I shows individual lipid values of the eight family members studied.

The Kindred

The pedigree of the members of the M family studied is shown in Figure 1. Relatives of prior generations were not available for study, but family history revealed that both parents of the father and one sister of the mother had died of cardiac causes between 35 and 40

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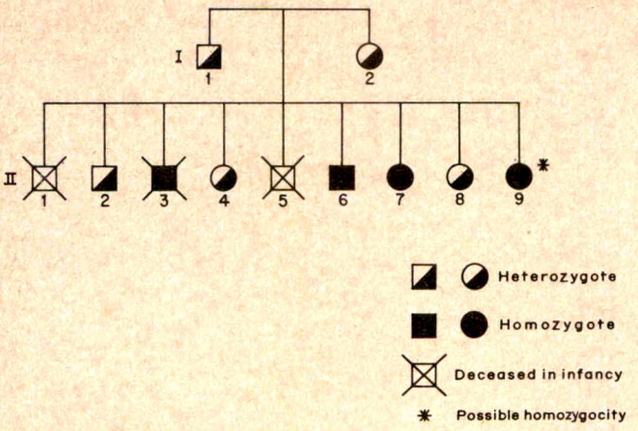

FIGURE 1. M family pedigree.

years of age. Both parents of this family had type II hyperlipoproteinemia with an elevated serum cholesterol level, but they had no xanthomatosis or clinical evidence of ischemic heart disease. All six children still living had hypercholesterolemia. Two of them (Patients II-6 and II-7) are homozygotes with xanthomatosis and are described in detail. Of the remaining four children, three (Cases II-2, II-4 and II-8) were considered heterozygotes and had hypercholesterolemia without xanthomas or cardiovascular disease. The remaining child (Case II-9), 2 months of age, had an abnormal cholesterol level for her age and may be a homozygote (Table I). One of the three children who died (Case II-3) had xanthomas, but the cause of death was transfusion of incompatible blood. The other two (Cases II-1 and II-5) died at a very early age, and their cholesterol levels were not available.

TABLE I

Individual Serum Lipid Levels

Subject	Age (yr) & Sex	Serum Cholesterol (mg/100 ml)	Serum Triglycerides (mg/100 ml)	Type Hyperlipoproteinemia
I-1	50M	382	195	IIb
I-2	40F	483	150	IIa
II-2	21M	305	195	IIb
II-4	16F	392	150	IIa
II-6*	11M	724	117	IIa
II-7*	9F	784	77	IIa
II-8	7F	352	112	IIa
II-9	2/12F	187	120	IIa

* Patients described in present report.

The Patients

Patient II-6: This 11 year old boy had tuberous and planar xanthomas in the buttocks at age 3 years. Xanthomas subsequently appeared in the interdigital regions of hands and feet as well as in the elbows and knees. Painful xanthomas also developed in the extensor tendons of the hands, elbows and heels (Fig. 2, A and B). On admission, July 1, 1971, the boy had a 6 month history of exertional dyspnea and typical effort angina pectoris characterized by oppressive chest pain relieved by rest and nitroglycerin, pallor and diaphoresis with occasional fainting spells. These symptoms did not keep him from his habitual duties, shining shoes and selling newspapers. A protosystolic aortic click was heard, followed by a grade 2/4 early and midsystolic basal ejection murmur, radiating to both carotid arteries. A loud second sound was also heard in the aortic area. The phonocardiogram suggested aortic valve thickening and revealed an ejection time at the upper limit of normal. Other recorded sounds included an apical opening mitral snap and a grade I systolic murmur radiating to the axilla. Bilateral arcus cornea was present. Blood pressure was 125/60 mm Hg with normal peripheral pulses.

After discharge, the patient's angina became more frequent and severe. Six months later a myocardial infarction developed, which was treated at another hospital. No signs of heart failure or hypotension were reported. He was discharged 6 weeks later and returned to his previous activities despite severe angina pectoris on effort. Symptoms and signs of progressive congestive heart failure developed in June 1973. On September 20, he was admitted for a second time with anasarca, digitalis intoxication and poor general condition; he was discharged on October 16 after control of his heart failure was effected.

Chest X-ray films in 1971 showed a heart of normal size with a thin layer of calcification in the aortic wall. During his last admission in 1973 grade III cardiomegaly was found (Fig. 3, A and B). No coronary arterial or valvular calcifications were seen. Radiolucent subperiosteal lesions and pseudocysts were observed in X-ray films of the hands and feet.

The electrocardiogram taken at rest in 1971 was consistent with a diaphragmatic and anterolateral subendocardial lesion (Fig. 4). Chest pain, diaphoresis and fainting occurred during a double Master exercise test that revealed

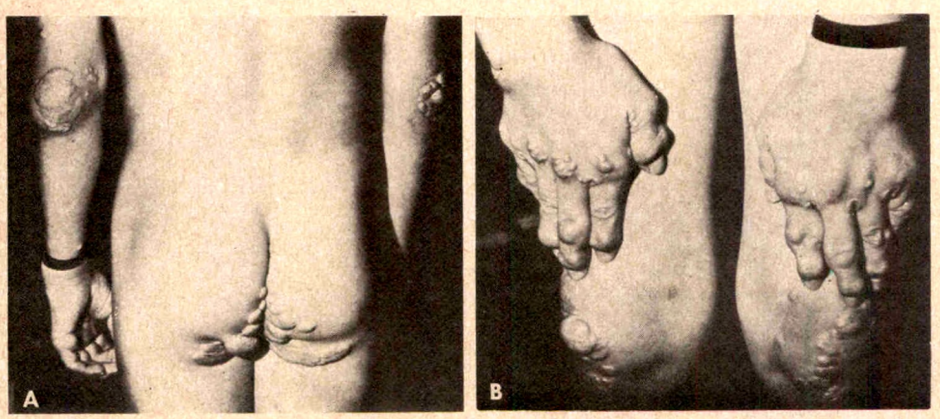

FIGURE 2. Patient II-6. Xanthomas.

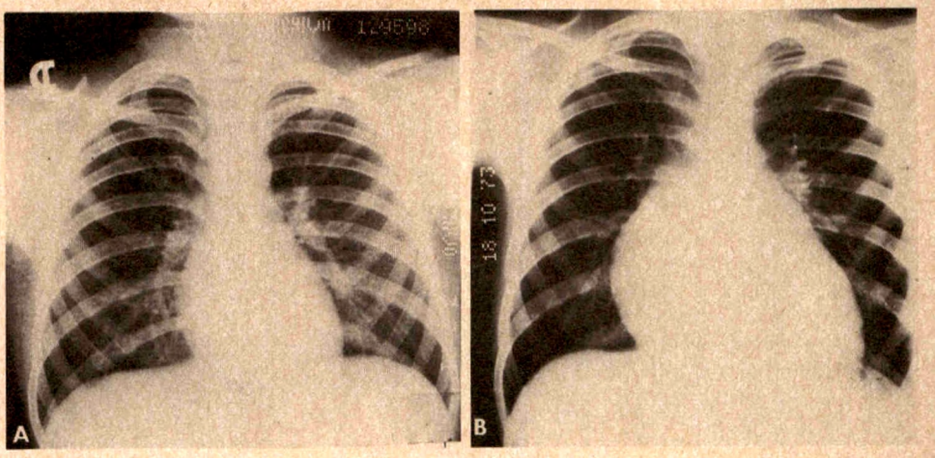

FIGURE 3. Patient II-6. Chest X-ray films: **A,** July 3, 1971 and **B,** October 18, 1973.

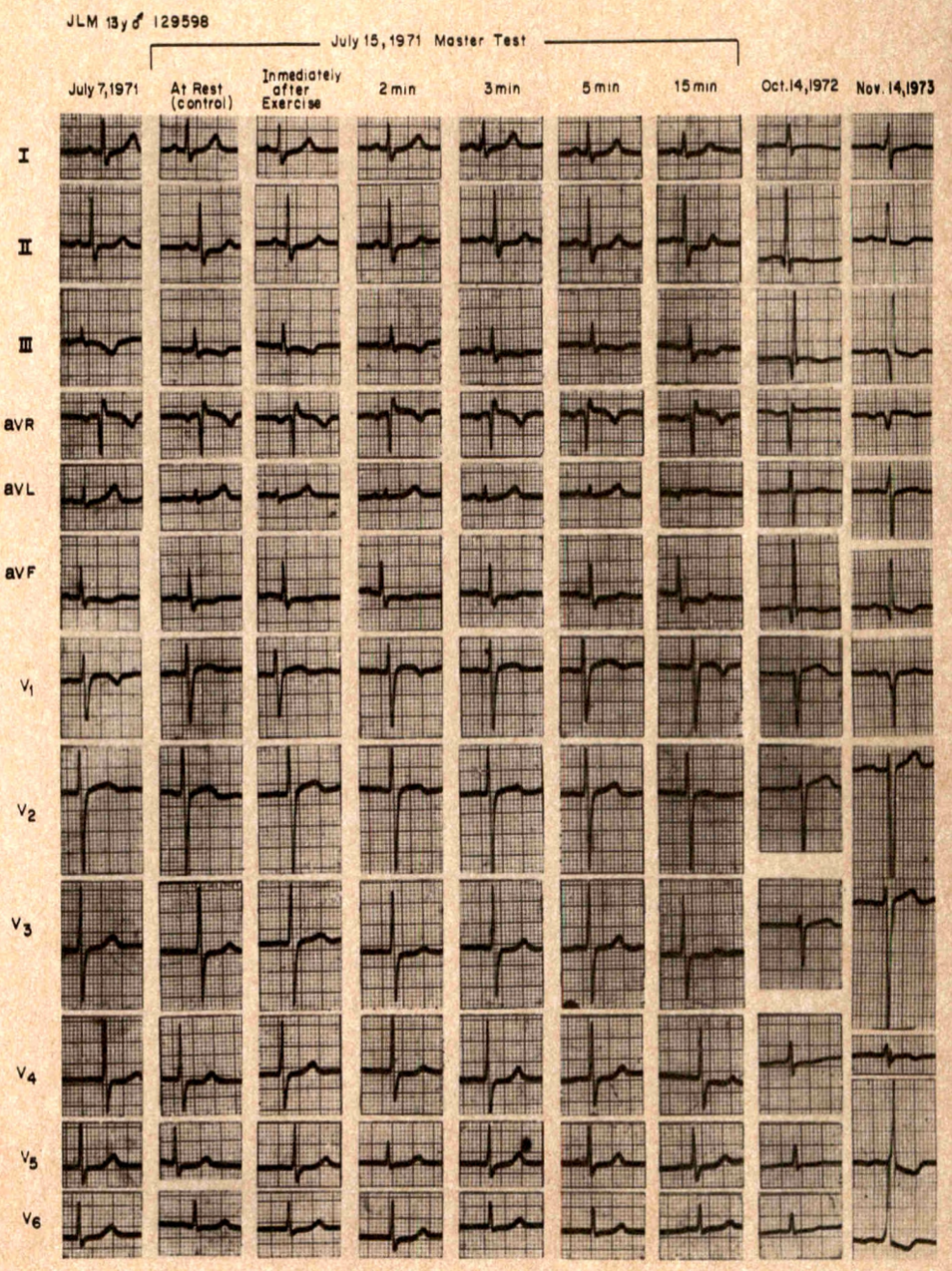

FIGURE 4. Patient II-6. Serial electrocardiograms.

transient increase of the diaphragmatic and anterolateral subendocardial lesion (leads V_3 to V_4) (Fig. 4). A postinfarction electrocardiogram in October 1972 revealed necrosis of the diaphragmatic wall and findings suggestive of midanteroseptal necrosis (smaller R wave in lead V_3 than in lead V_2). On his last admission in 1973, besides the old diaphragmatic infarction, a left posterior hemiblock with right axis deviation and subendocardial lesion of the lateral wall were evident (Fig. 4).

Cardiac catheterization and coronary arteriography with use of the Mason Sones technique were performed on July 20, 1971. Left ventricular systolic pressure was 142 with an end-diastolic pressure of 7 and mean pressure of 93 mm Hg; there was no gradient across the aortic valve during systole. Coronary arteriography revealed normal right (Fig. 5A) and circumflex coronary arteries. There were two areas of at least 90 percent narrowing in the left anterior descending artery (Fig. 5B). Left ventricular cineangiogram disclosed synergistic contraction with no evidence of mitral regurgitation and normal systolic ejection fraction. In a second study performed on October 30, 1973 there was complete obstruction of the right and left anterior descending coronary arteries (Fig. 5, C and D). Few collateral vessels were visualized and there was no distal filling. The left circumflex coronary artery was normal (Fig. 5D). No left ventricular angiogram was obtained because of the development of pain and pulmonary edema. However, a phonokinetocardiogram revealed extensive dyskinesia of the anterior left ventricular wall and elevated *a* wave with a short ejection period. Ventricular dyskinesia was also seen during fluoroscopy.

A psychologist considered the patient hyperkinetic with a reactive depressive syndrome and schizoid personality.

Patient II-7: This 9 year old girl had tuberous xanthomas as an early manifestation at age 3 years. On admission she was asymptomatic and had multiple tuberous, planar and tendinous xanthomas. Arcus cornea was absent. Her blood pressure and peripheral pulses were normal. An early systolic ejection murmur with normal ejection time and delayed ascending limb of the carotid pulse was recorded, suggestive of aortic valve thickening. Chest X-ray films and cardiac fluoroscopic studies were normal. Electrocardiograms were normal at rest and after a double Master exercise test. Cardiac catheterization revealed a left ventricular systolic pressure of 137, end-diastolic pressure of 8 and a mean of 65 mm Hg. The aortic pressure was 137/73 mm Hg with a mean of 94. There was no gradient across the aortic valve during systole. Coronary angiography and ventriculography revealed normal arteries and left ventricle.

Because of the patients' lack of cooperation no adequate therapeutic (diet and drug) trial was possible in either child.

Discussion

Familial type II hyperlipoproteinemia is a hereditary disease related to a highly penetrant autosomal dominant gene.[3,8,9] The homozygous phenotype is characterized by a high serum level of low density lipoprotein (LDL).[3,8,10] Serum cholesterol level is more than 500 mg/100 ml in adults and more than 100 mg/100 ml in the umbilical cord.[11–13] Xanthomas ap-

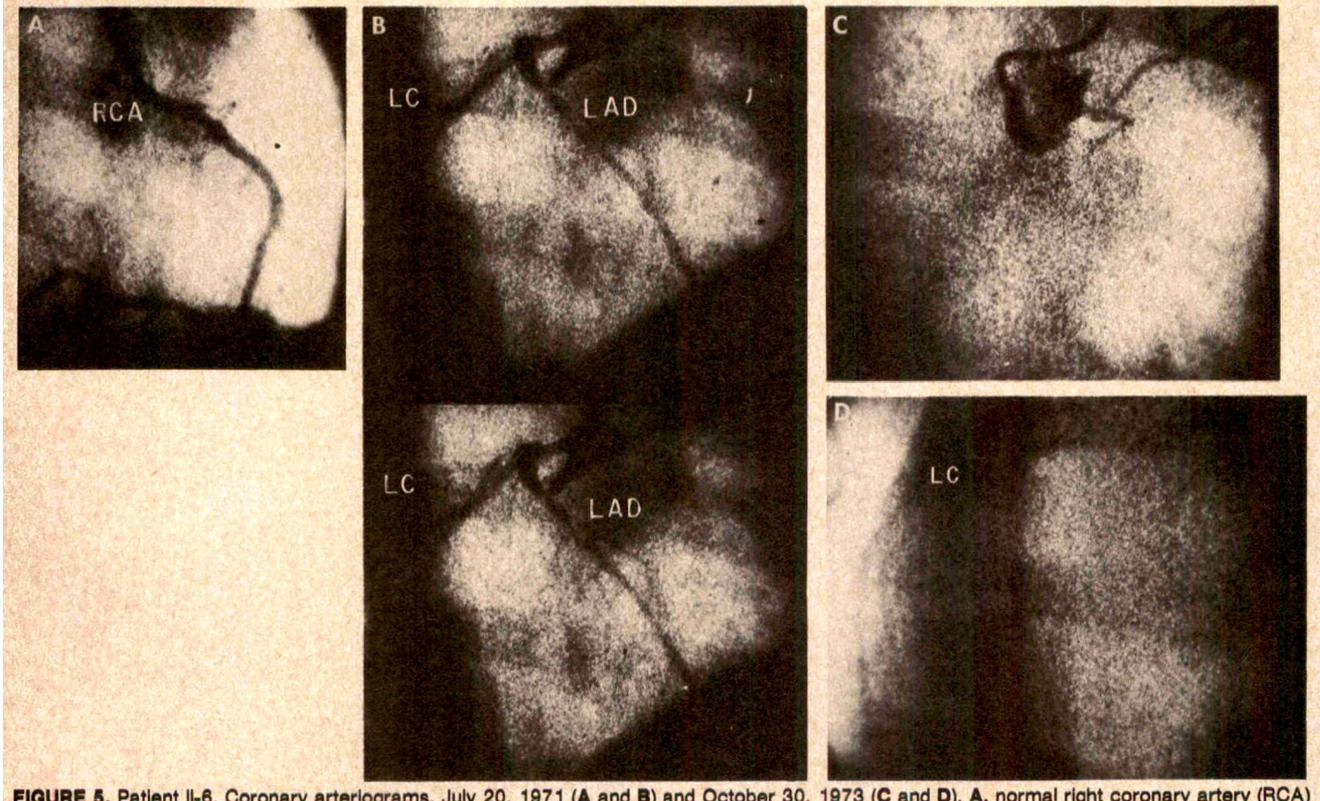

FIGURE 5. Patient II-6. Coronary arteriograms, July 20, 1971 (**A** and **B**) and October 30, 1973 (**C** and **D**). **A,** normal right coronary artery (RCA) and **B,** two areas of proximal narrowing in the left anterior descending coronary artery (LAD). Normal left circumflex artery (LC). **C,** total obstruction of the right coronary artery. The atrial artery is visualized. **D,** complete obstruction of the anterior descending coronary artery. Normal left circumflex artery is seen (LC).

pear before age 10 years and vascular disease is common before age 20 years.[3] This is apparently due to hypocatabolism of cholesterol-rich betalipoproteins, and no defect in synthesis or distribution has been demonstrated.[8,14,15] It is the most frequent familial genetic disorder[8] and may be found in 1 of every 150 to 200 live births.[8,12] Survival is known to be limited to the second or third decade.[3,16–32] Obstruction of the major extramural coronary arteries by atherosclerotic plaques has been found at autopsy in more than 75 percent of cases examined.[8,16,17,21,29]

Our patients had all the characteristics of the homozygous type II phenotype. In Patient II-6 early and progressive obstruction of the coronary arterial tree was objectively documented by means of coronary arteriography. The first study disclosed severe narrowing of the left anterior descending artery although the right and the left circumflex coronary arteries were normal. Two years later, however, complete obstruction had developed in the left anterior descending and the right coronary arteries. This is highly suggestive of progression of coronary atheromatosis, although the occlusion could also have been caused by an embolic plaque or thrombosis in situ. In any case, this course of events makes us believe that aortocoronary bypass surgery would be difficult to consider since the rapid progression of atheromas and occlusion cannot be altered by surgery. In fact, if this patient had had a bypass to the left descending coronary artery the surgeon could not have predicted the obstruction of the right coronary artery that also developed.

The lack of collateral circulation or visible small vessels is noteworthy. It is not known whether their absence is related to the rapid development of the obstruction of the main arteries, or to involvement of the small vessels of the myocardium, or both.

Aortic atherosclerosis in homozygous type II hyperlipoproteinemia is greater in the ascending than in the abdominal portion of the aorta.[3,10] This "reverse" distribution is mostly circumscribed at the ascending aorta, supravalvular, valvular or subvalvular portion, and can also include the endocardium of the left ventricle, mitral valve and atrial endocardium.[10,23] Sometimes the right heart structures are also involved, such as the major pulmonary arteries[10,28] and the tricuspid valve.[3,11] Signs of lipid deposits with thickening of the aortic valves were recorded in our two cases, although an aortic-ventricular gradient was not obtained. These findings could be considered as the initial step in the development of valvular aortic stenosis since the aortic cusps have been reported to be thickened, with the orifice narrowed and sometimes heavily calcified.[19,20,25,27,30–32] Supraaortic stenosis has also been described.[10] Atherosclerotic plaques at the mural endocardium of the left ventricular outflow tract have sometimes produced subaortic stenosis.[11,33] The presence of lipid-calcified deposits at the coronary ostium[10] should always be kept in mind when performing coronary arteriographic studies. As suggested in Patient II-6, mitral involvement is possible, although it has not been reported to produce stenosis or insufficiency of the valve.[3,10,21,29]

Addendum

Patient II-6 had chest pain and died with ventricular fibrillation December 20, 1974.

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Coronary Artery Disease in an 18 Year Old Girl with Pseudoxanthoma Elasticum: Successful Surgical Therapy

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An 18 year old girl with pseudoxanthoma elasticum, a 7 year history of angina pectoris and evidence of an old anteroseptal myocardial infarction was found on coronary angiography to have three vessel coronary artery disease. A triple coronary artery-saphenous vein bypass graft was performed, and she has been asymptomatic for 1 year. Histologic examination of a segment of the right coronary artery revealed changes consistent with the vascular lesion of pseudoxanthoma elasticum.

Pseudoxanthoma elasticum is an inherited connective tissue disease in which the basic defect is thought to be a dysplastic and metabolic derangement of elastic tissue.[1,2] Fragmentation and calcification of elastic tissue in the peripheral vessels is a well known feature of the disease.[3] However, associated disease of the coronary arteries has been recognized previously only at autopsy,[2,4–6] by roentgenographic calcification[7] and, on one occasion, by coronary angiography.[8]

This report describes an 18 year old girl with pseudoxanthoma elasticum who had had classic angina pectoris since the age of 11. Coronary angiography demonstrated severe three vessel coronary artery disease, and all symptoms of ischemic heart pain were totally relieved after a triple coronary bypass graft procedure. A biopsy of the coronary artery at the time of surgery revealed vascular changes similar to those previously described in postmortem studies of pseudoxanthoma elasticum.[1]

Case Report

An 18 year old white girl was referred to this hospital for evaluation of chest pain of 7 years' duration. She first became aware of chest pain at age 11 while walking up stairs at school. The pain was described as a substernal pressure occurring predictably with physical exertion and relieved by rest. The pain never lasted more than a few minutes, was relieved by sublingually administered nitroglycerin, and was often associated with dyspnea, palpitations and sweating. The pain had gradually increased in frequency and occurred 5 to 10 times a day, depending on the level of her activity. In high school her activities were markedly restricted, and she was allowed to have most of her classes on the first floor. There was no past history of rheumatic fever or chest trauma. She had scarlet fever at age 10 years, when it was first noted that she had a yellowish papular skin rash on her neck, which has persisted to the present time. In October 1970 she had an episode of nausea, vomiting and pain in the right upper quadrant without melena that was diagnosed as acute gastroenteritis. She denied knowledge of hypertension or diabetes and was not taking oral contraceptive agents. She has smoked 20 cigarettes a day for about 4 years.

The family history is pertinent in that the patient's 20 year old brother has a similar rash on the neck that has been diagnosed as pseudoxanthoma elasticum. He is asymptomatic. Her mother and father are second cousins. The father is living and had a myocardial infarction at age 52.

On physical examination she appeared well and in no acute distress. Temperature was 98.6° F, heart rate 72 beats/min, respiratory rate 15/min and

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FIGURE 1. Photograph demonstrating the typical yellowish papular rash of pseudoxanthoma elasticum over the anterior neck.

blood pressure 120/80 mm Hg. Examination of the skin revealed loose, moderately redundant, inelastic skin over the anterior aspect and both sides of the neck. Yellowish firm papules were arranged in linear fashion over these areas (Fig. 1). The dermatologic consultant believed these lesions to be diagnostic of pseudoxanthoma elasticum. There were no xanthomas. Examination of the eyes revealed diffuse angioid streaks of both fundi, most prominent in the right eye at 1, 5 and 9 o'clock (Fig. 2). The jugular venous pressure and wave contour were normal, as was the carotid arterial upstroke. The chest was clear to auscultation and percussion.

Examination of the heart revealed the point of maximal impulse to be located at the midclavicular line in the left fourth interspace. The first heart sound was normal, the second was physiologically split, and no third or fourth heart sound was heard. There was a grade 1/6 systolic ejection murmur at the left second intercostal space, but no precordial heaves or paradoxic bulges were present. There was an extrasystole approximately every 5 to 10 beats. Examination of the abdomen revealed no abnormality. All pulses were present and normal bilaterally in the limbs.

Laboratory Studies

Laboratory values were hemoglobin 13.6 g/100 ml, hematocrit 38.3 percent and white blood cells 8,130 mm^3 with a normal differential count. Urinalysis revealed a specific gravity of 1.025, no albumin or sugar and a normal sediment. The erythrocyte sedimentation rate was 10 mm in 1 hour. All routine blood chemistry and serum enzyme values were normal. The prothrombin time was normal. Results of the Hinton serologic test were negative. Values for fasting serum cholesterol and triglyceride were 188 mg/100 ml and 106 mg/100 ml, respectively; the serum uric acid level was 4 mg/100 ml. The lipoprotein electrophoresis was normal. The fasting glucose value was 83 mg/100 ml, and results of an oral glucose tolerance test were normal.

The resting electrocardiogram revealed a sinus rhythm of 70 beats/min with 6 to 12 premature ventricular beats per minute. There was a small q wave in leads V_1 to V_3. The S-T segments were flat and depressed by 0.5 mm in leads I, II and V_4 to V_6. The T waves were biphasic in leads II and V_4 to V_6. A Master two step test was performed and revealed 2 mm S-T segment depressions in leads V_4 to V_6 and chest pain was produced. The vectorcardiogram confirmed an old anteroseptal myocardial infarction.

The cardiac X-ray series revealed no evidence of cardiac chamber enlargement, no calcification and a normal pulmonary vasculature. An echocardiogram revealed normal mitral valve excursions. Results of an X-ray series of the upper gastrointestinal tract were normal, and X-ray examination of the arms and legs revealed no evidence of vascular calcification.

Cardiac catheterization and coronary arteriograms: Cardiac index was normal (4.0 liters/min per m^2) as were the pulmonary arterial pressure (25/8 mm Hg) and other right-sided pressures. The systemic pressure was 124/75 mm Hg. There were no valvular gradients, and the left ventricular end-diastolic pressure was normal. Right atrial pacing was performed to a rate of 144 beats/min. The patient did not experience angina, but her left ventricular end-diastolic pressure increased abnormally to 16 mm Hg at the cessation of pacing. The left ventricular angiogram

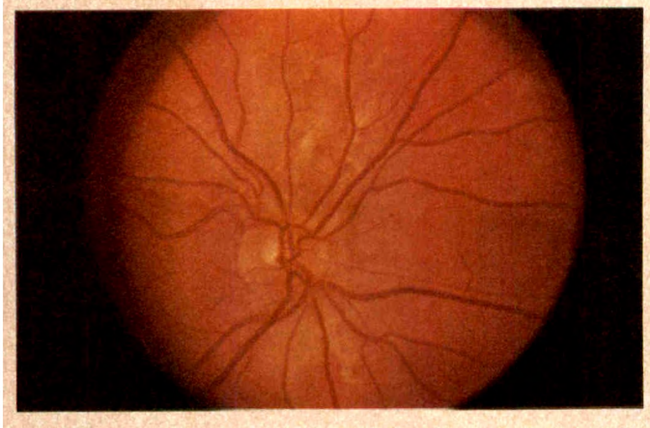

FIGURE 2. Ophthalmoscopic appearance of ocular fundus. **Left,** showing angioid streaks in inferior and superior nasal quadrants and superior temporal quadrant. **Right,** angioid streaks after staining with fluorescein.

revealed inferoapical hypokinesia and the systolic ejection fraction was 50 percent.

The selective coronary arteriograms revealed a complete occlusion in the proximal third of the right coronary artery with distal reconstitution by way of collateral vessels from both the left and right coronary arterial systems (Fig. 3). There was a greater than 75 percent stenosis of the proximal third of the left anterior descending coronary artery, and a 90 percent stenosis of the distal third of the left circumflex coronary artery. The distal left circumflex artery filled retrogradely from collateral vessels (Fig. 3).

Clinical Course

Because of the frequency and severity of her symptoms, her age, the presence of three vessel coronary disease and evidence of abnormal ventricular performance, the patient was considered a candidate for coronary bypass surgery.

At the time of surgery, the coronary arteriographic findings were confirmed. The proximal third of the right coronary artery was found to be a firm cord, and a 5 mm long biopsy specimen was obtained for histologic studies. The right coronary artery distal to the obstruction was small (internal diameter 1.5 mm). One saphenous vein graft was anastomosed in a side to side fashion to the mid-portion of the right coronary artery, and continued as an end to side anastomosis to a 2 mm posterior ventricular branch of the left circumflex artery. A second graft was anastomosed proximally to the ascending aorta and distally to the left anterior descending artery beyond the stenosis. The measured flow in the first and second grafts as the patient came off the cardiopulmonary bypass pump was 115 and 165 ml/min, respectively. The postoperative course was uneventful except for premature ventricular contractions that occurred at a rate of 5 to 10/min in the 1st 24 hours postoperatively; the arrhythmia responded to intravenous administration of lidocaine hydrochloride. The patient was discharged on the 10th postoperative day and has thus far remained asymptomatic. When seen 1 year postoperatively, she had married, recently become pregnant and had experienced no ischemic chest pain since the operation.

Histologic Studies

A skin biopsy specimen taken from the area of her neck rash revealed an increase in elastic fibers in the mid and lower dermis associated with dermal fibrosis. As demonstrated with a Verhoeff-van Gieson stain, these intradermal elastic fibers were thickened and fragmented (Fig. 4A).

A right coronary arterial biopsy obtained during coronary bypass surgery revealed a markedly narrowed lumen due to both subendothelial thickening and medial fibrosis (Fig. 4B). The subendothelial connective tissue was rich in acid mucopolysaccharide, as demonstrated by both alcian

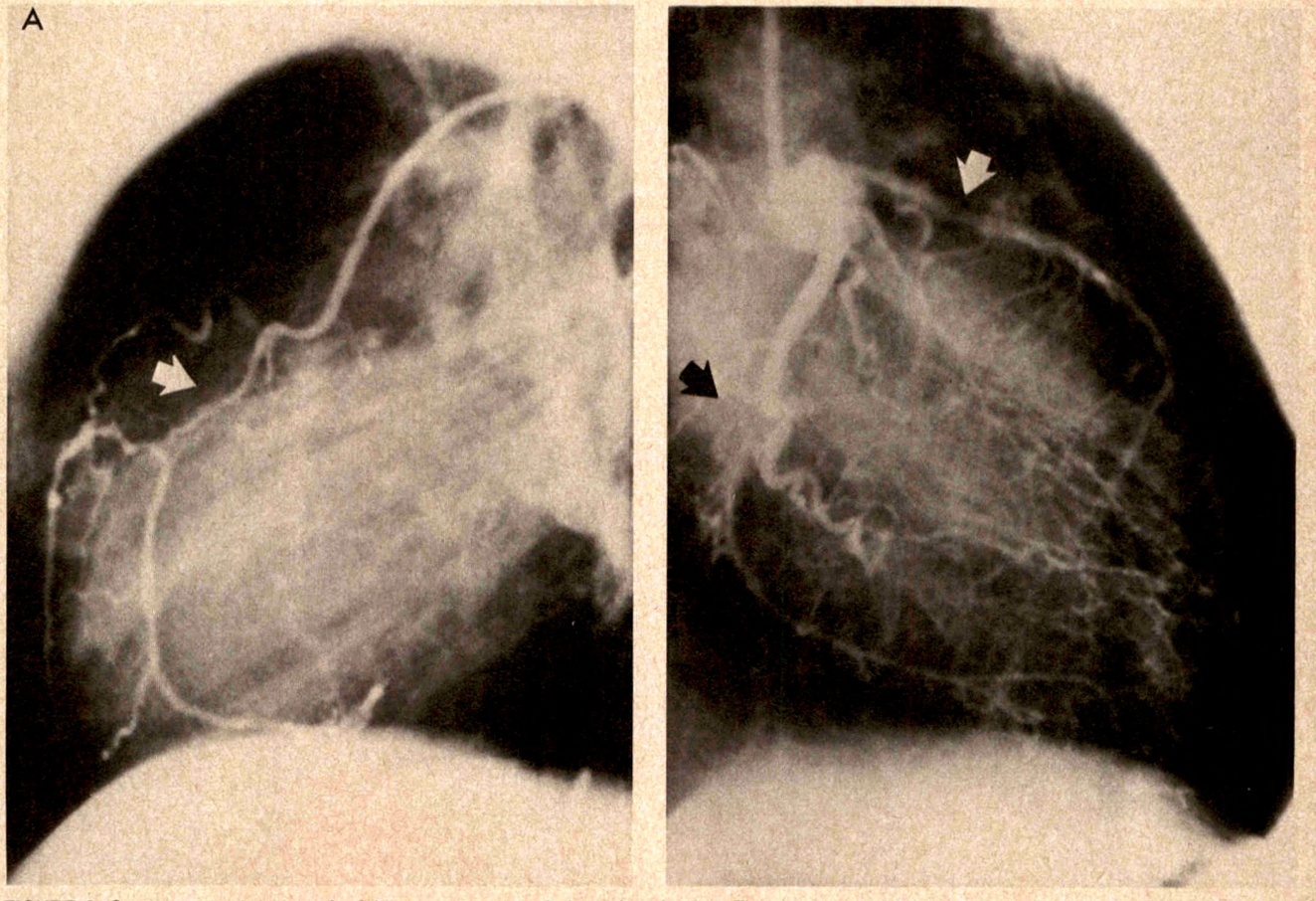

FIGURE 3. Coronary arteriograms. **A,** right coronary artery in lateral projection. There is a complete segmental occlusion in the proximal third **(white arrow).** Distal filling occurs from a large conus branch and the acute marginal artery. **B,** left coronary artery in the right anterior oblique projection. An occlusive lesion **(white arrow)** is visible in the proximal portion of the left anterior descending branch. The distal portion of the left circumflex branch reveals 90 percent stenosis **(black arrow)** with collateral filling of the distal segment.

blue and Hale's dialyzed iron stains; it also contained clumps of coarse elastic fibers. The internal and external elastic laminae were disrupted and fragmented. Dense foci of calcification were also found in the media (Fig. 4C).

Biopsy of the right atrial appendage revealed mild interstitial fibrosis. Along the endocardium were foci of plaque-like areas composed of dense connective tissue with prominent curled and fragmented elastic fibers (Fig. 4D).

Biopsies of the proximal left femoral and saphenous vein disclosed normal findings; however, a biopsy of the ascending aorta revealed a mild increase in elastic fibers with irregular thickening and fragmentation.

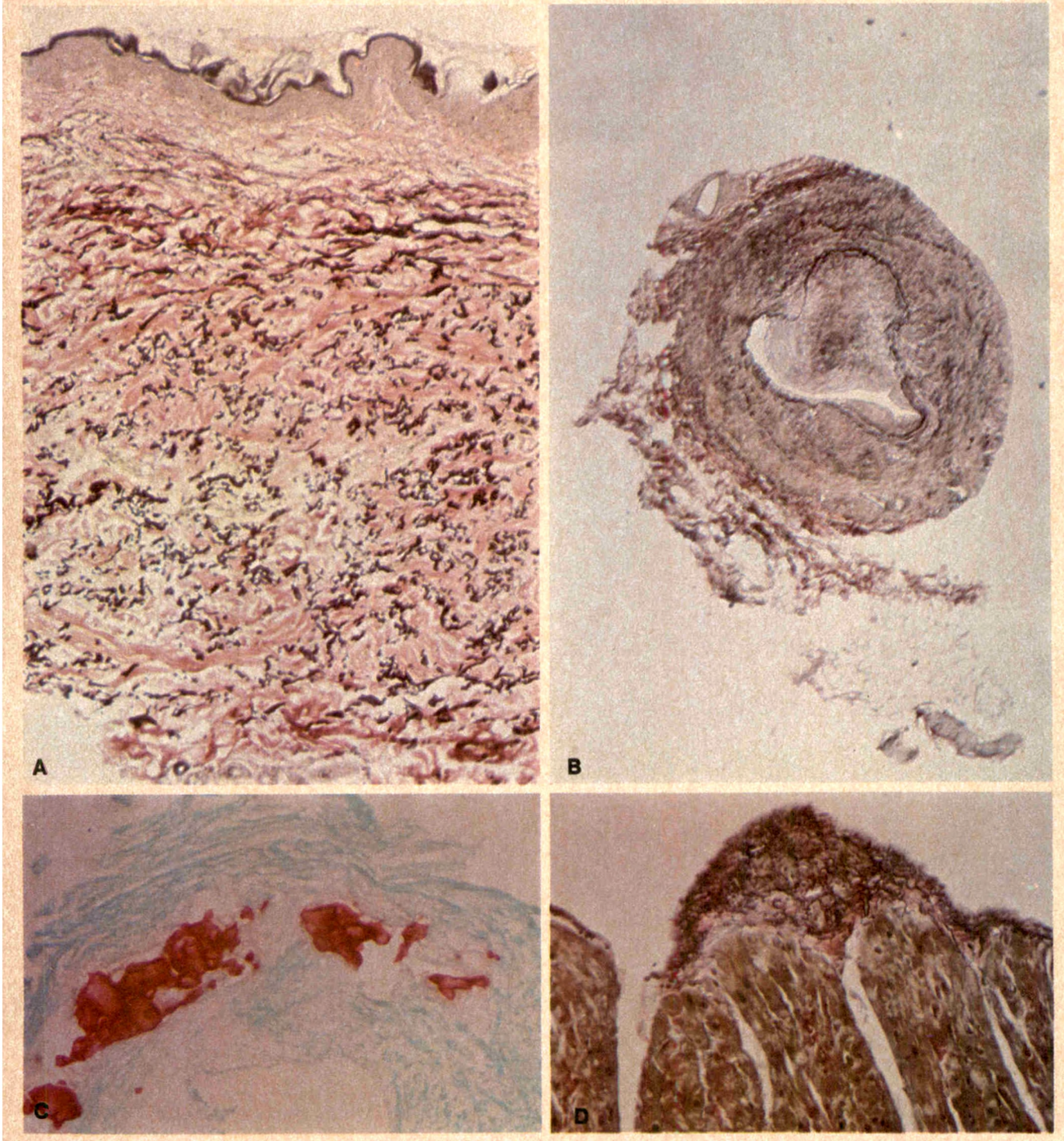

FIGURE 4. Biopsy sections. **A,** section of skin from the neck area demonstrating intradermal fibrosis and a marked increase in fragmented elastic fibers (stained black). **B,** section of the right coronary artery with severe luminal narrowing, asymmetric subendothelial thickening, disruption of elastic laminae and increased elastic fibers in the media. **C,** dense calcification (stained red) demonstrated in the media of the coronary artery. **D,** right atrial appendage showing a plaque-like elevation along the atrial endocardial surface containing prominent curled elastic tissue fibers. **A** and **B,** Verhoeff-van Gieson X63 and X25, respectively, increased by 355 percent; **C,** alazarine red ×160, increased by 235 percent; **D,** Verhoeff-van Gieson ×160, increased by 235 percent.)

Discussion

Our patient has clinical and laboratory findings consistent with the diagnosis of pseudoxanthoma elasticum. Her predominant symptom was debilitating angina pectoris of 7 years' duration. Although her angina never lasted more than 3 to 4 minutes, her electrocardiogram and vectorcardiogram revealed an anteroseptal myocardial infarction, and selective coronary arteriography demonstrated significant obstructive disease of all three major vessels.

Because of the absence of the known risk factors of coronary heart disease in a young woman, other causes of coronary artery disease such as anomalous coronary vessels, left ventricular outflow obstruction and vasculitis were ruled out during the diagnostic evaluation. A recent report[9] describes two sisters less than 20 years old with occlusive coronary artery disease resulting from advanced intimal fibrous proliferation. However, our patient had no evidence of this abnormality on coronary arterial biopsy. In light of these observations and the histologic appearance of the right coronary artery, it is clear that our patient suffered from coronary occlusive disease secondary to the vascular lesions of pseudoxanthoma elasticum.

Cardiovascular abnormalities in pseudoxanthoma elasticum: Pseudoxanthoma elasticum is a multisystem disease involving predominantly the skin, eyes, gastrointestinal tract and cardiovascular system.[5,10] Peripheral vascular involvement is common in both the arms and legs.[3,11,12] The basic abnormality is believed by most authorities to involve abnormal elastic fibers that appear to have an unusual affinity for calcium.[1,2] This results in elastic fiber shortening, wrinkling, degeneration and marked calcium deposition, particularly in the media of the arteries; subintimal and medial fibrosis occurs, which eventually narrows the lumen. Although the peripheral vascular manifestations have been well described, evidence of coronary artery disease has been less thoroughly investigated.

Coronary arterial involvement: In the first case examined at autopsy by Balzer[13] in 1884, endocardial thickening was described in the right atrium and ventricular myocardium, but no coronary arterial findings were noted. More recently, Coffman and Sommers[14] and Huang et al.,[15] have described cases of pseudoxanthoma elasticum with pathologic involvement of the endocardium and valves. In 1959, Carlborg et al.[16] reported angina in 15 of 29 patients with pseudoxanthoma elasticum. Angina developed at an early age in these patients. The mean age of the group with angina was 38 years, and one patient with angina was only 7 years old. In subsequent reported series the incidence rate of angina has ranged from 4 to 50 percent.[2,17] Although angina has been described in patients with pseudoxanthoma elasticum, myocardial infarction is rare.[8] In 1958, Nellen and Jacobson[7] first reported radiologic evidence of calcification of the coronary arteries in a 31 year old woman with pseudoxanthoma elasticum who had no cardiac symptoms and a normal electrocardiogram. Hamilton-Gibbs[18] recently reported myocardial infarction in a 6 week old infant whose mother had pseudoxanthoma elasticum. At autopsy, widespread calcification of all coronary arteries was found, and obliteration of the left main coronary artery and the left anterior descending branch were seen. However, no definite diagnosis of pseudoxanthoma elasticum was made in the infant.

Ours is the third patient with pseudoxanthoma elasticum studied by coronary angiography. McKusick[5] described a patient with substernal chest pain and a normal electrocardiographic exercise test who also had a normal coronary arteriogram. Maurice and Capronnier[8] described a 23 year old man with pseudoxanthoma elasticum who had severe angina pectoris and a previous inferolateral myocardial infarction. The coronary arteriogram revealed total occlusion of the left anterior descending coronary artery and diffuse lesions distally in the right coronary artery. Prick[4] described a patient at postmortem examination with tissue abnormalities of pseudoxanthoma elasticum in the coronary arteries. Goodman et al.[2] reported three cases of pseudoxanthoma elasticum in which the external elastic membrane in the coronary arteries contained broken and irregular calcified elastic fibers. McKusick[5] described autopsy findings in a 13 year old patient with gastrointestinal hemorrhage and in a 63 year old man with severe coronary disease. Both cases were believed to manifest changes in the coronary arteries unique to pseudoxanthoma elasticum.

Vascular and coronary bypass surgery: There are few accounts of vascular surgery in patients with pseudoxanthoma elasticum, and no previous reports of coronary arterial surgery. For this reason there was concern about the technical aspects of the surgical procedure, particularly with regard to tissue healing and the competence of the graft anastomosis. However, in view of McKusick's description[5] of successful homograft procedure in a patient with pseudoxanthoma elasticum and a typical Leriche syndrome secondary to thrombotic obliteration of the bifurcation of the aorta, our patient was advised to undergo coronary arterial bypass surgery.

At operation all tissues and vessels with the exception of the occluded right coronary artery appeared grossly normal and handled normally, enabling routine vein grafts to be placed. Healing proceeded normally, and at follow-up examination 1 year later the patient was asymptomatic.

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Multiple Ventricular Aneurysms

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Angiocardiographic study of a case of multiple ventricular aneurysms in a 17 year old Nigerian girl is reported. The patient presented with ventricular tachycardia and has remained well after conversion of the arrhythmia to sinus rhythm. The pathogenesis of multiple ventricular aneurysms is briefly reviewed.

Myocardial infarction is the most common cause of aneurysms of the left ventricle in temperate climates, where coronary artery disease represents a major medical problem. Aneurysms that occur after myocardial infarction usually appear singly, are composed of elements of infarcted myocardium and represent bulging of the weakened wall.

The rarity of coronary artery disease in the African has been the subject of many communications[1–4] although aneurysms of the left ventricle have been encountered and documented in Nigerians.[5,6] However, in each case, these aneurysms occurred multiply and the patients, when first seen, either had congestive heart failure with evidence of mitral regurgitation or had findings indicative of systemic embolism. We report a case of multiple aneurysms of the left ventricle found in an apparently healthy young girl with no symptom suggestive of cardiac disability.

Case Report

The patient is a 17 year old school girl whose only complaint on admission to the Cardiovascular Clinic of Lagos University Teaching Hospital was palpitations. She had had episodes of palpitations during the previous 3 years but they had not been of consequence. She had never had fainting attacks, exertional dyspnea or angina pectoris.

On examination, the only abnormalities found were a pulse rate of 186/min and a blood pressure reading of 90/50 mm Hg. There was no cardiomegaly or heart murmur, and there were no signs of congestive heart failure.

An electrocardiogram (Fig. 1) revealed ventricular tachycardia that reverted to normal (Fig. 2) after intravenous injection of 50 mg of lidocaine. There were inverted T waves in leads II, III and aVF and flat T waves in leads V_5 and V_6. A chest X-ray examination performed on the same day (Fig. 3) revealed abnormal intracardiac calcification suggestive of either calcified dermoid cysts or ventricular aneurysms.

Cardiac catheterization was performed. A yellow Kifa catheter was introduced into the right femoral artery by the Seldinger technique and advanced retrograde into the left ventricle. A no. 7 Cournand catheter was introduced into the right femoral vein by the same technique and advanced into the pulmonary artery. Pressures were recorded on an Electronics for Medicine DR 8 recorder, using a P23 Db strain gauge; cardiac output was measured by the Fick principle. All pressures were within normal limits. Left ventricular end-diastolic pressure was 5 to 10 mm Hg and increased after angiography to 16 to 18 mm Hg. Cardiac output was 5.8 liters/min. However, the left ventriculogram (Fig. 4), showed three pockets of ventricular aneurysms, one of which was calcified and filled, possibly with clots.

The patient has remained well and symptom-free on a maintenance dose of quinidine, 200 mg twice daily.

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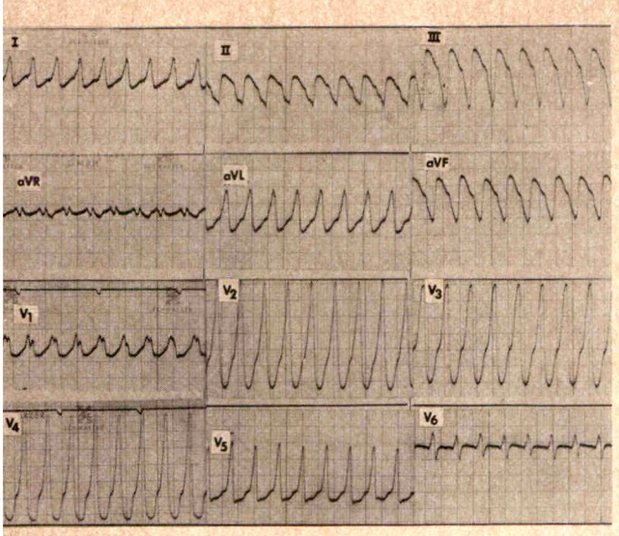

FIGURE 1. Electrocardiogram on admission, revealing ventricular tachycardia.

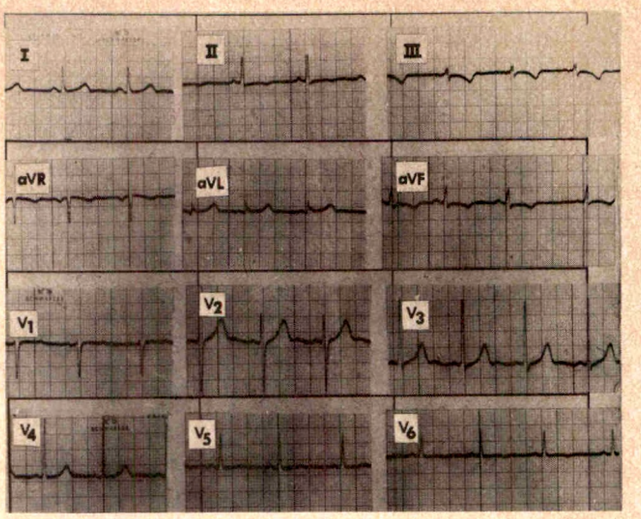

FIGURE 2. Electrocardiogram after reversion of tachycardia to sinus rhythm following administration of 50 mg of lidocaine.

Discussion

Multiple ventricular aneurysms form an interesting group of cardiac aneurysms, and virtually all the cases previously described have been in African Negroes who are free of coronary artery disease. Abrahams et al.[5] from Ibadan reported that all six of their patients had heart failure and most had mitral insufficiency and cardiomegaly. Electrocardiograms showed T wave changes suggestive of myocardial disease. Our patient probably represents the first instance of a patient who was in good health and has remained asymptomatic during 3 years of observation. Unless systemic embolism or fatal arrhythmias occur, her prognosis is probably good.

The pathogenesis of multiple ventricular aneurysms is poorly understood. Edington and Williams[7] observed in a study of 12 autopsy cases that the coronary arteries were patent and relatively free of atheromas. Histologically, they found that a few hearts had focal aggregates of lymphocytes in the myocardium, and that two manifested a chronic type of endocarditis affecting the mitral valve. They therefore suggested that an infectious origin cannot be entirely excluded, although they admitted that the apparent limitation of these aneurysms to Africans is difficult to explain with this hypothesis. It is possible, however, that these aneurysms also occur in Europeans and Americans but are mistaken for postinfarction aneurysms.

Chesler[8] has suggested that multiple aneurysms of the left ventricle may be due to a congenital defect in those portions of the aortic or mitral valve anulus that are directly related to the epicardium and in which there is a muscular-fibrous junction. These are the areas where the ostia of the aneurysms are found in cases studied at autopsy, but again it is difficult to

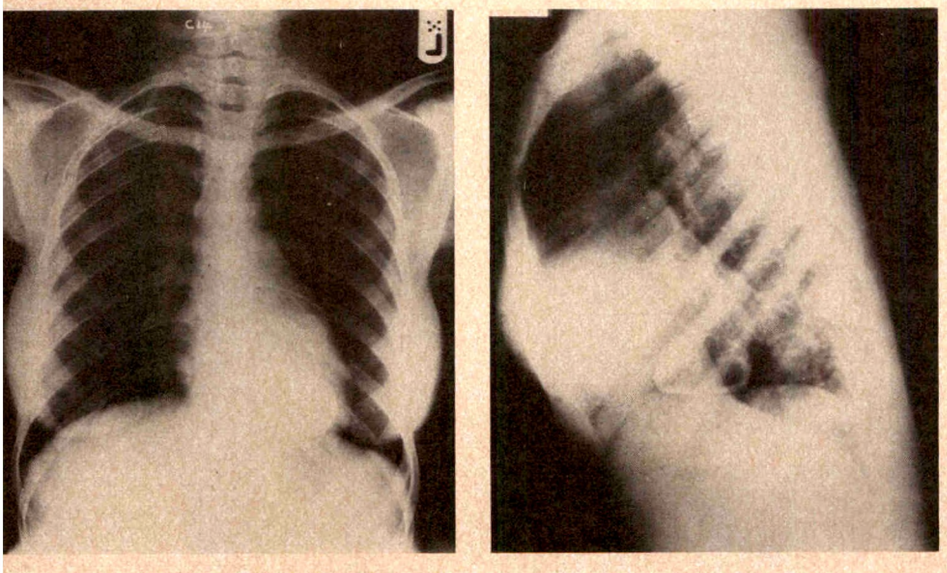

FIGURE 3. Chest X-ray films in posteroanterior **(left)** and lateral **(right)** views, revealing abnormal intracardiac calcifications suggestive of calcified dermoid cysts or ventricular aneurysms.

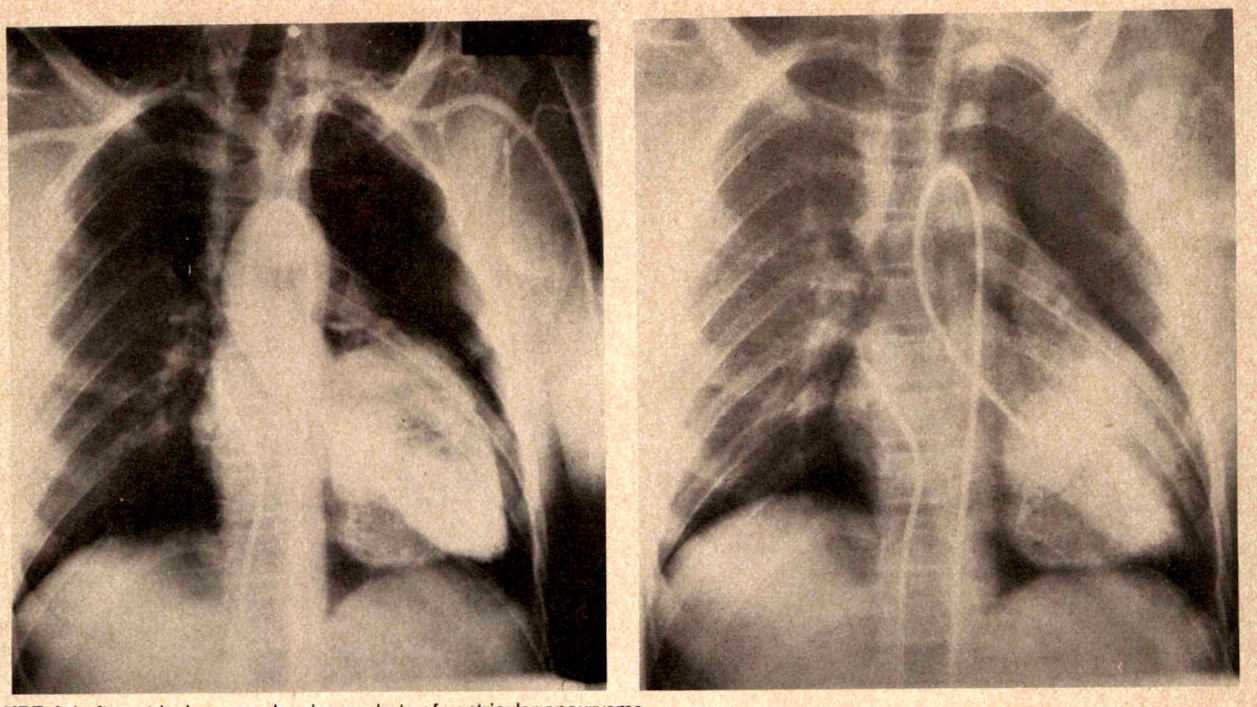

FIGURE 4. Left ventriculograms showing pockets of ventricular aneurysms.

explain why this "congenital" defect should be limited to Africans.

One must also consider the more common occurrence of primary myocardial disease of unknown origin in Africans. In the advanced stages of this disease patients have severe resistant congestive heart failure with gross cardiomegaly, mitral insufficiency and pulmonary hypertension—findings shared by the patients with ventricular aneurysms described by Abrahams et al.[5] Angiograms performed in some of these cases of primary myocardial disease revealed not only poor myocardial contractility, but also some completely akinetic areas suggestive of pseudoaneurysms. It is therefore possible that whatever etiologic factor is responsible for diffuse myocardial damage in congestive cardiomyopathy may also affect some patients in a patchy fashion, resulting in areas of weakened walls that after a few years develop into aneurysms.

If this is the case, our patient, who now has good cardiac function, in subsequent years may show evidence of poor myocardial contractility and congestive cardiac failure similar to that of patients with primary myocardial disease. This event would lend support to the view that these two diseases have a common pathogenesis.

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Herniation of Mitral Leaflets in the Ehlers-Danlos Syndrome

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A 47 year old patient with the Ehlers-Danlos syndrome (hypermobility of the joints, hyperextensibility of the skin and atrophic cutaneous scars) was evaluated because of a mitral regurgitant murmur and paroxysmal atrial tachycardia. Angiocardiography and echocardiography demonstrated marked systolic herniation of the posterior leaflet of the mitral valve. An echocardiogram from the patient's daughter, who also had paroxysmal atrial tachycardia, revealed the same abnormality. Although a "floppy" valve is common in Marfan's syndrome, this report emphasizes that it may also occur in patients with other heritable disorders of connective tissue.

The Ehlers-Danlos syndrome is a heritable disorder of connective tissue characterized by fragility and hyperextensibility of the skin, hypermobility of the joints and a variety of visceral abnormalities.[1] The clinical findings are relatively specific, and generally the syndrome is easily distinguished from other heritable disorders of connective tissue. However, patients with the Ehlers-Danlos syndrome and those with Marfan's syndrome occasionally share certain characteristics, including laxity of articular structures, ectopia lentis, high arching of the palate, skeletal deformities and cystic medial necrosis of the aorta and other major arteries.[1]

In patients with Marfan's syndrome retroversion of the mitral cusps with valvular insufficiency (the "floppy valve syndrome")[2,3] may occur on the basis of myxomatous transformation of the leaflets or chordae tendineae.[2,4,5] The floppy valve syndrome has also been noted with the Ehlers-Danlos syndrome,[1] although reports of this association are sparse. However, the presence of a large amount of connective tissue in the fibrous skeleton of the heart, chordae tendineae and valve cusps suggests that structural cardiac abnormalities might not be rare in the Ehlers-Danlos syndrome.

This report describes a patient with the Ehlers-Danlos syndrome who had mitral regurgitation due to atrial herniation of the posterior leaflet of the mitral valve. It suggests that defects of the valve leaflets or chordae tendineae may be a manifestation of the Ehlers-Danlos syndrome.

Case Report

A 47 year old man was admitted to this hospital on April 28, 1972 for evaluation of a cardiac murmur, intermittent palpitations and progressive fatigue. A heart murmur had been noted at age 5 years during a routine examination and again at age 19 years when he was accepted for military service. There was no history of rheumatic fever.

He tired easily but had no history of significant exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, cough, syncope or angina pectoris. For 12 years before admission he had had occasional episodes of palpitations lasting for minutes to days that required his hospitalization on three occasions. An electrocardiogram taken in 1971 during the last such episode revealed paroxysmal atrial tachycardia. The attacks were successfully controlled by administration of digoxin.

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FIGURE 1. Hypermobility of the wrist.

All his life the patient has been "loose-jointed" and complained of aching in the hands, wrists, elbows, knees, ankles and neck, aggravated by physical exertion. He has never had morning stiffness or joint swelling. He had a whiplash injury of the neck in 1969 but has not experienced frequent sprains or joint dislocations.

There was no history of friable skin, easy bruisability or poor wound healing. Epistaxis occurred four to six times each year, requiring cauterization on several occasions. At age 16 years the patient underwent bilateral saphenous vein ligations for varicosities.

The patient's father had died suddenly at home at age 40 years of an "internal hemorrhage" of unknown origin. Unfortunately, we have been unable to examine relatives of the propositus. According to the patient, no family members were unusually tall or thin. A brother, aged 61 years, allegedly has genu recurvatum. A sister, aged 45 years, is reportedly normal, but two of her five children are "double-jointed."

Of the patient's six children, a 16 year old daughter has been known to have a heart murmur since age 7 years and has paroxysmal atrial tachycardia. She has no history of rheumatic fever. A phonocardiogram, performed at age 15 years, revealed multiple midsystolic clicks and a late systolic crescendo murmur at the apex. An echocardiogram disclosed increased mitral valve excursion (3 cm) and systolic prolapse of the posterior leaflet of the mitral valve into the left atrium.

On examination the patient was 183 cm tall and weighed 57.7 kg. His arm span was 173 cm and his lower segment length (symphysis pubis to floor) 91 cm (upper segment to lower segment ratio = 1.0). There was no suggestion of arachnodactyly or dolichostenomelia. The fingers and elbows could be readily subluxed and, with flexion of his wrists, the patient was able to touch his thumb to the forearm (Fig. 1). With extension of the shoulders, both scapulae met in the midline. Both hip joints could be extended to 25°. Dynamic pes planus was present bilaterally. A bony deformity of the left elbow existed at the site of a fracture sustained in childhood, but there was no swelling, limitation of motion or tenderness of any other joints. The skin was smooth and velvety with abnormal extensibility and elasticity, particularly over the neck, elbows, forearms and

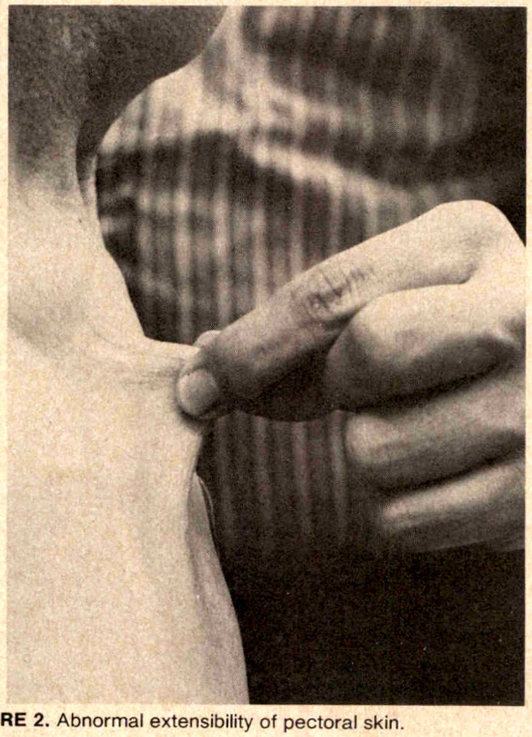

FIGURE 2. Abnormal extensibility of pectoral skin.

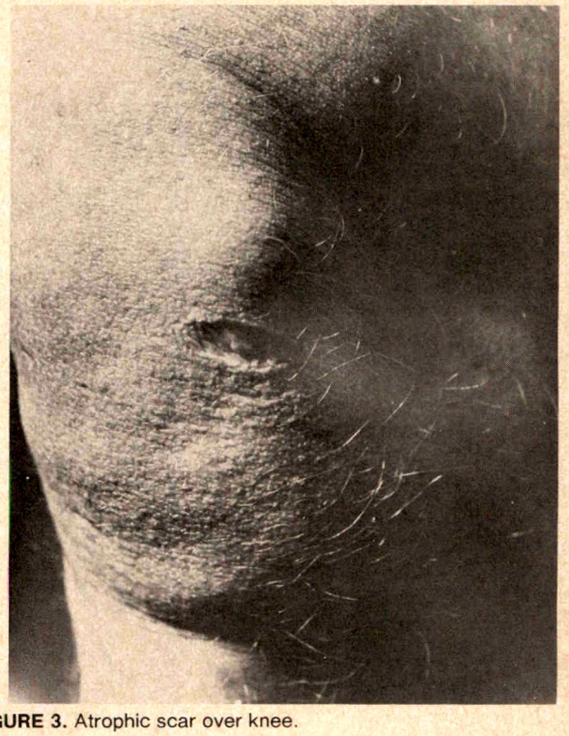

FIGURE 3. Atrophic scar over knee.

chest (Fig. 2). There were atrophic "cigarette paper" scars over the right knee (Fig. 3) and at the sites of the incisions from previous saphenous vein ligations. No subcutaneous nodules or molluscoid tumors were found.

The sclerae were not blue, and there was no iridodonesis. Adductor rectus muscle weakness was present bilaterally. Slit lamp examination confirmed the absence of lenticular subluxation.

The palate was extremely highly arched. No abnormality of the nasal mucosa was seen. The anteroposterior diameter of the thorax was increased and the thorax was asymmetric, with prominence of the left anterior side of the chest. The dorsal spine was straight, with loss of the normal kyphosis. Both diaphragms were low but moved normally. The chest was hyperresonant. No rales or rhonchi were noted.

The blood pressure was 120/80 mm Hg in both arms and the heart rate 80 beats/min and regular. The peripheral pulses were normal. No cyanosis, malar flush or abnormal jugular venous distension was present. The cardiac apical impulse was diffuse and maximal in the sixth intercostal space in the midclavicular line. A systolic thrill was felt at the apex. The first heart sound was loud and the second heart sound normal and physiologically split. A ventricular diastolic gallop was heard at the apex. No clicks were present. A grade 4/6 holosystolic murmur, heard maximally at the apex, radiated to the left axilla. A grade 1/6 early diastolic decrescendo blowing murmur was heard at the left sternal border.

The complete blood count, urinalysis and serum electrolyte values were within normal limits, and the Westergren erythrocyte sedimentation rate was 3 mm in 1 hour. The platelet count was 200,000/mm^3. Prothrombin time, partial thromboplastin time, thrombin time and fibrinogen level were all normal. Platelet function tests revealed normal adhesiveness to a glass bead column and normal aggregation after exposure to thrombin, collagen, adenosine diphosphate and epinephrine.

X-ray films of the cervical spine disclosed anterior subluxation at the level of the fifth cervical vertebra, with straightening and loss of the normal cervical lordosis below that level. A pseudoarthrosis was present between the spinous processes of the first two cervical vertebrae. X-ray films of the chest revealed marked elongation of the thorax with flattening of the diaphragms. The third rib was bifid. The spine was straight, with loss of the normal thoracic and lumbar curves. The fifth thoracic vertebra was wedged anteriorly. The cardiac silhouette was normal. No pulmonary vascular congestion or cardiac valvular calcifications were seen. X-ray films of the hands were normal; the metacarpal index[6] was 7.75.

The vital capacity was 5,700 ml (152 percent of predicted) and the maximal breathing capacity 92 liters/min (85 percent of predicted). The expiratory reserve volume was 1,950 ml, residual volume 2,140 ml, functional residual capacity 4,090 ml and carbon monoxide diffusing capacity (D_LCO) 23.2 ml/min per mm Hg (71 percent of predicted).

Cardiac studies: The electrocardiogram revealed sinus rhythm with a rate of 75/min. The P-R and QRS intervals were 0.26 and 0.09 second, respectively. The P waves were somewhat broad and peaked and there was evidence of left anterior hemiblock. Vectorcardiography confirmed the left anterior hemiblock and indicated P pulmonale. A phonocardiogram confirmed the auscultatory findings of the physical examination.

The echocardiogram revealed an augmented mitral valve excursion of 3.4 cm, and a normal anterior leaflet velocity of 104 mm/sec. Prolapse of the posterior leaflet into the left ventricle could be seen in early systole[7] (Fig. 4A). The aortic root was dilated, with a diameter of 5.1 cm (Fig. 4B).

Catheterization of the left and right heart chambers demonstrated no valvular gradients or evidence of intracardiac shunting. The height of the *V* wave in the pulmonary capillary wedge pressure tracing was 10 mm Hg, and all other pressures were normal. Cardiac index was 2.3 liters/min per m^2.

Left cineventriculograms were obtained in both oblique projections and demonstrated a normal chamber size and contractions. Reflux of contrast medium into the left atrium was estimated to be 2+ and clearly outlined marked herniation of the posterior leaflet of the mitral valve during systole (Fig. 5A). This was followed by a wide diastolic ex-

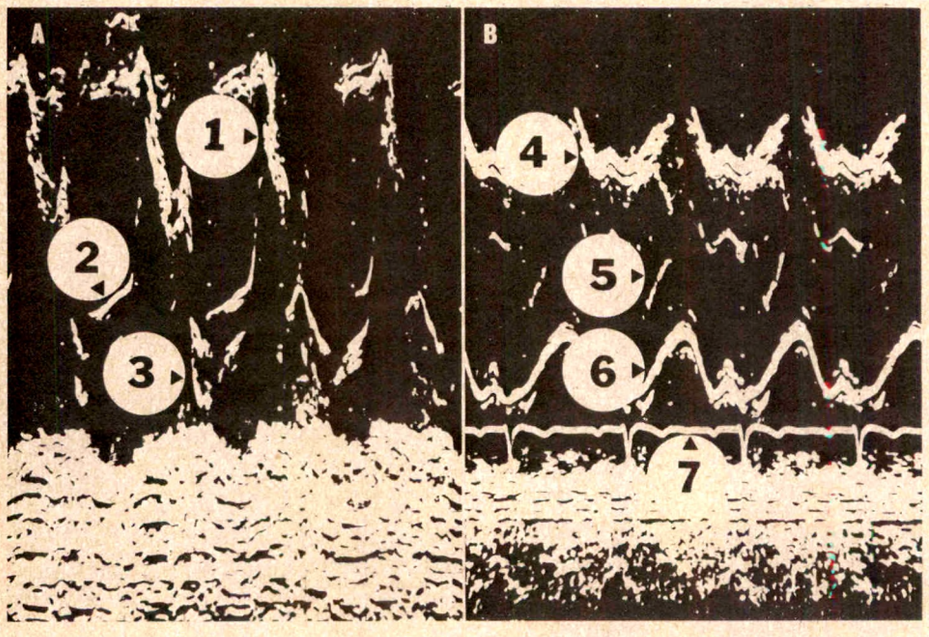

FIGURE 4. Echocardiograms. **A,** (1) E point of the anterior leaflet of mitral valve revealing an augmented excursion of 3.4 cm; (2) midsystolic position of the anterior leaflet of the mitral valve; (3) early systolic prolapse of the posterior leaflet of the mitral valve into the left atrium at the onset of ventricular systole. **B,** (4) anterior portion of the aortic root; (5) aortic valve echo in systole; (6) posterior wall of the aortic root with a diastolic dimension of 5.1 cm; (7) electrocardiogram.

cursion of the herniated leaflet. Aortic root angiography revealed dilatation of the sinuses of Valsalva and trace amounts of aortic regurgitation (Fig. 5B). Selective coronary cinearteriography revealed a normal right dominant system with no evidence of obstructive disease.

Discussion

Extreme joint laxity, cutaneous hyperextensibility, "cigarette paper" scars, a tendency to hemorrhage and development of varicose veins in youth, and a family history of similar abnormalities are all hallmarks of the Ehlers-Danlos syndrome.[1,8] We have been unable to find reports of pulmonary function studies in patients with this disease, but the greatly augmented vital capacity (152 percent of predicted) in our case reflects an extraordinary degree of compliance of the thorax and pulmonary parenchyma, suggesting that they were affected by the same abnormality that involved the skin and joints. Thus, our patient fulfilled all the clinical criteria for the generalized connective tissue disorder recognized as the Ehlers-Danlos syndrome.

The cineangiographic studies provided direct evidence that the mitral regurgitation in our patient was due to prolapse of the posterior mitral leaflet into the left atrium. Because angiography may carry an increased risk of complications in patients with the Ehlers-Danlos syndrome,[9] it is notable that the herniated posterior mitral cusp was also readily detected by echocardiography[7] in this case.

The anatomic abnormalities responsible for herniation of the mitral leaflets were not elucidated. A variety of factors—such as rupture of chordae tendineae due to bacterial endocarditis, or papillary muscle dysfunction due to coronary artery disease—may produce prolapse of the mitral valve,[10,11] but there were no grounds to support such diagnoses in our patient. Furthermore, occlusive coronary artery disease was excluded by selective coronary cinearteriography. It is therefore possible that the valve leaflet was inherently lax and redundant, or the chordae tendineae were lengthened, or both, as a result of the underlying connective tissue defect.

Cardiac defects in Ehler's-Danlos Syndrome: A review of 100 cases of the Ehlers-Danlos syndrome[12] has led to the conclusion that if a specific cardiac defect occurs it must be very uncommon. Isolated reports of other patients with the Ehlers-Danlos syndrome have described conventional cardiac defects, such as tetralogy of Fallot,[13] atrial septal defect,[14] partial persistent atrioventricular canal[15] and bicuspid right atrioventricular valve.[16] Whether these represent coincidental associations or whether the basic connective tissue abnormality predisposes to defects in ontogeny is not known.

Detailed reports of patients with the Ehlers-Danlos syndrome and herniation of the mitral valve are lacking. McKusick,[1] however, has noted signs of the condition in some patients with the Ehlers-Danlos syndrome, type III, that is, those having marked and generalized joint hypermobility but in whom hyperextensibility of the skin and other cutaneous manifestations are usually minimal. Our patient appears to have had considerably more skin involvement than is usual in such cases.

Differentiation from Marfan's syndrome: In Marfan's syndrome herniation of the mitral valve is due to myxomatous transformation.[2,3] The same pathologic lesion may also be seen in patients who themselves have no distinguishing skeletal characteristics but whose family members have arachnodactyly or dolichostenomelia, suggesting that the herniating mitral valve may be a forme fruste of Marfan's syndrome.[2] In contending that the valve lesion in our case may have been a feature of the Ehlers-Danlos syndrome, therefore, it is important to exclude the

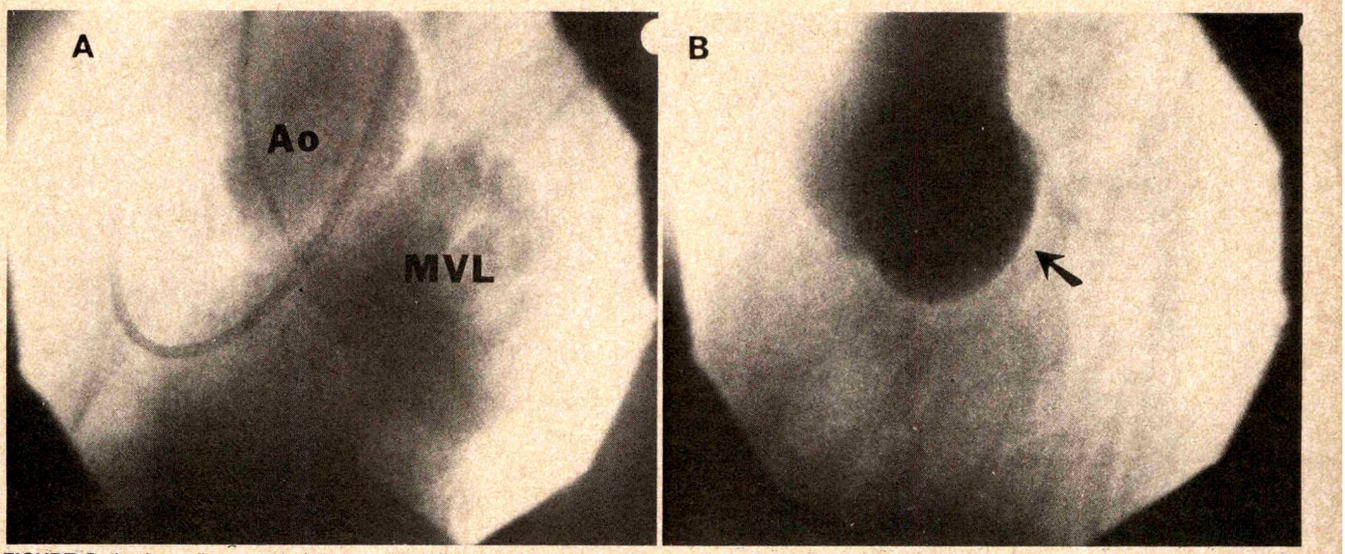

FIGURE 5. Angiocardiograms in left anterior oblique projection. **A,** cineventriculogram demonstrating systolic herniation of the posterior mitral valve leaflet (MVL) into the left atrium. Scalloping of the leaflet can be noted. **B,** aortic root angiogram demonstrating dilatation of the sinuses of Valsalva **(arrow).**

possibility that the patient also had Marfan's syndrome. Indeed, the concurrence of these two heritable connective tissue diseases has been reported in a kindred[17] and patients have been described who have both the body habitus of Marfan's syndrome and the skin and joint changes of the Ehlers-Danlos syndrome.[18]

There is no evidence that our patient had Marfan's syndrome; he did not have arachnodactyly, abnormalities of other skeletal proportions or the lenticular subluxation typical of that disorder. Although his palate was highly arched and his sinuses of Valsalva were dilated, these findings are common to both Ehlers-Danlos and Marfan's syndromes and therefore not of value in differentiating between the two disorders.[1] Perhaps the most significant point in excluding the diagnosis of Marfan's syndrome in our case is the absence of a positive family history of Marfan's syndrome, whereas members of at least two generations demonstrated the skin hyperextensibility and joint laxity characteristic of the Ehlers-Danlos syndrome.

Paroxysmal tachycardia: The evidence of a herniating mitral leaflet in the patient's daughter is of particular interest. Previous reports[19] have suggested that this condition is sometimes genetically determined. Moreover, the occurrence of paroxysmal atrial tachycardia in both the propositus and his daughter may be related to their mitral valve abnormality, since arrhythmias are not uncommon in patients with herniating mitral valves.[20] In this regard it is notable that in Marfan's syndrome arteries to the sinoatrial and atrioventricular nodes may show medial degeneration and hyperplasia and intimal proliferation.[21] The histologic features of the conducting system in the Ehlers-Danlos syndrome has not been studied, but may be similar.

Bacterial endocarditis: Finally, bacterial endocarditis has a tendency to develop in patients with Marfan's syndrome and the floppy mitral valve syndrome.[22,23] By analogy, in view of the findings in our case, antibiotic prophylaxis at times of increased risk, such as dental extraction, appears to be warranted in patients with the Ehlers-Danlos syndrome who have evidence of cardiac valve disease.

Acknowledgment

We are grateful to Dr. Kirwan T. MacMillan for referring this patient for study. Dr. Lila Talarico kindly performed the tests of platelet function and Dr. Michael Freed generously provided copies of the echocardiograms and phonocardiograms of the propositus's daughter. We thank Mr. David Feigenbaum for his expert photographic assistance.

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Dynamic Ventriculography and the Role of the Ejection Fraction

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Cardiac function is best evaluated in two different states since function may be normal at rest and abnormalities may become evident only when a load or stress is applied to the cardiovascular system. Such an intervention is exercise, typically used to provoke changes in the electrocardiogram or phonocardiogram, particularly when these are normal at rest. Similarly, hemodynamics have been studied in the cardiac catheterization laboratory at rest and during exercise.[1,2] These studies have concerned changes in pressures and flow, but not in the function of the heart as a pump, primarily because of the limitations of technique for quantifying the displacement capabilities of the beating heart. The advent of ventriculography allowed changes in wall motion and ventricular volume to be evaluated throughout the cardiac cycle. Most recently, the pumping action of the left ventricle has been analyzed, not only at rest but during a second state designed to test the reserve capacity of the heart in a manner similar to that of the earlier studies of pressure and flow. *Dynamic ventriculography* is the term that best characterizes this type of investigation.

Types of Dynamic Ventriculography

In most instances, two left ventriculograms are required, the first under controlled conditions with appropriate measurements of heart rate and systemic (or pulmonary) pressures. The purpose of the second study is either to precipitate latent dysfunction or to test contractile reserve. Methods of eliciting latent ventricular dysfunction include atrial pacing,[3–5] exercise[6,7] and infusion of propranolol.[8] Pacing-induced ischemia may be reflected by the induction of either segmental or generalized abnormalities of contraction. Thus, Dove et al.[5] reported abnormal wall motion during pacing in two patients with coronary artery disease and normal wall motion at rest, and worsening of wall motion during pacing in four of five patients with previous abnormalities. Pasternac et al.[3] reported that during pacing abnormal wall motion appeared in two of three patients with normal motion at rest, and previous wall motion abnormalities were made worse in six of seven other patients. Dwyer[4] reported similar findings and noted that diminished wall motion found in more than one segment reflected multiple coronary vessel involvement. In two preliminary reports, Flessas et al.[6] reported the same type of findings in 10 subjects studied before and during handgrip exercise, and Sharma and Taylor[7] in 8 subjects studied before and during dynamic leg exercise. Intravenous administration of propranolol also resulted in induced or exaggerated asynergy in 5 of 10 subjects studied by Helfant et al.[8] (The mechanism of action of propranolol is different from that of pacing or exercise and is presumably related to the drug's general cardiac depressant action.)

If contractile reserve of a normal or asynergic area is to be assessed, a catecholamine such as *l*-epinephrine may be infused or nitroglycerin administered sublingually. *l*-Epinephrine increases the contractile state of the myocardium, whereas nitroglycerin decreases the afterload against which the ventricle must eject. Infusion of *l*-epinephrine in 18 patients in our laboratory[9] resulted in improvement in wall motion in normal areas and in asynergic zones composed of muscle, or a mixture of muscle and scar, but not composed of scar alone. Results were similar in 35 patients studied with nitroglycerin by Helfant et al.[10] Dove et al.[5] reported normalization or improvement in wall motion after administration of nitroglycerin in six patients undergoing pacing at the same rates that had previously resulted in worsening of wall motion.

One technique that also measures contractile reserve, but requires only one ventriculogram, utilizes a ventricular premature beat, either induced or spontaneous, during the first few beats of the ventriculo-

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gram.[11] The beat following a ventricular premature contraction is potentiated (increasing the contractile state of the myocardium). The wall motion and volume of the potentiated beat can be compared with those of the beat preceding the ventricular premature contraction. In 18 patients postextrasystolic potentiation induced a response similar to that obtained with *l*-epinephrine, except that the degree of improvement was greater and more consistent.

Role of the Ejection Fraction in Dynamic Ventriculography

The ejection fraction is a useful measurement of ventricular pump function since it relates ventricular stroke volume to end-diastolic volume. As a single measurement, it is superior to left ventricular end-diastolic pressure, which may be influenced by both ventricular volume and compliance, and to cardiac output, which is itself a function of unrelated variables, including venous return, aortic impedance, heart rate and stroke volume. Ejection fraction has been reported to be useful in the evaluation of patients with congenital heart disease,[12] cardiomyopathy,[13] valvular heart disease[14,15] and coronary artery disease.[15,16] By assuming the left ventricle to be ellipsoidal, and using the area-length method[17] to determine ventricular volumes, it is relatively simple to obtain the ejection fraction from the ventriculogram. Since ventriculography is becoming more and more a routine part of the standard diagnostic cardiac catheterization, the ejection fraction is as readily available as conventional measurements of pressure and cardiac output. Unlike the isovolumic pressure-time indexes, it requires no special equipment. Furthermore, in comparing measurements of ventricular dysfunction, sophisticated indexes such as contractile element velocity (V_{CE}) and contractile element velocity at zero load (Vmax) seem to hold no advantages over measurements based on emptying or displacement from the ventricle.[18] The mean rate, or velocity, of circumferential fiber shortening (V_{CF}), which relates transverse axis shortening to ejection time, is theoretically superior to ejection fraction. However, since ejection time is usually relatively constant from patient to patient, there is often no clinical advantage to using this variable instead of the ejection fraction.

The proved value of the ejection fraction as a hemodynamic measurement of overall left ventricular function and as a prognostic guide to clinical outcome makes it a useful measurement to be assessed during dynamic ventriculography. Determination of the ejection fraction in two states—at rest and during an intervention—helps to define change in the global character of the heart as a pump in the same way that measuring segmental axial shortening defines changes in segmental performance. For example, Pasternac et al.[3] demonstrated a decline in ejection fraction of six of eight patients with coronary artery disease who manifested asynergy or worsening of previously asynergic areas during tachycardia induced by right atrial pacing. Ejection fraction was unchanged in two patients with coronary artery disease who did not manifest asynergy. Similarly, Dwyer[4] showed a decline in ejection fraction in 8 of 10 patients with coronary artery disease who manifested asynergy or worsening of asynergy during right atrial pacing. During handgrip exercise, Flessas et al.[6] reported that 8 of 10 patients had a reduced ejection fraction in conjunction with development of hypokinesia. Therefore, when dynamic ventriculography is used to precipitate latent left ventricular dysfunction, a reduction in the left ventricular ejection fraction is usually associated with development or worsening of regional wall motion abnormalities. Sometimes this is minor but, as both Pasternac[3] and Dwyer[4] have pointed out, in many patients a decline in ejection fraction may be dramatic and suggests serious impairment of left ventricular function during tachycardia-induced ischemia.

Improvement in contractile reserve can also be demonstrated by observing changes in ejection fraction during dynamic ventriculography. Ejection fraction improved in 2 normal control subjects and 12 of 16 patients with coronary artery disease after infusion of *l*-epinephrine.[9] Similarly, during postextrasystolic potentiation, ejection fraction was improved in 3 normal control subjects and all 15 patients with coronary artery disease.[11] Augmentation greater than 0.10 was not unusual in both series. The change in overall ejection fraction during inotropic stimulation with epinephrine or postextrasystolic potentiation, or both, was examined in patients with ischemic heart disease with a depressed ejection fraction at rest.[19] The results were correlated with immediate and short-term prognosis after either surgical or medical treatment with or without preexisting congestive heart failure. Increases in ejection fraction greater than 0.10 were associated with a better prognosis than were lesser degrees of augmentation ($P < 0.001$). Furthermore, after myocardial revascularization, segmental zones that had exhibited increased shortening during inotropic stimulation[20] or administration of nitroglycerin[10] often showed improvement over the preoperative resting state when repeat left ventriculograms were performed.

In all studies, reproducibility of the technique as well as the effects of contrast medium must be taken into consideration.[21,22] Ventriculograms should be programmed at the same degree of obliquity with the camera and at the same distance from the patient and tabletop for all sequential studies. They should be analyzed according to standardized conventions, preferably by the same observer. Reliance on automated or semiautomated techniques may eliminate some of these problems in the future although at present there is no uniformity of opinion regarding reference points for superimposition of end-diastolic and end-systolic silhouettes to allow for measurement of *segmental* areas of wall shortening. Hemodynamic monitoring should be employed routinely before each ventriculographic study since alterations in ventricular configuration or emptying, or both, may

be due to changes in heart rate, preload, afterload or contractile state in association with, or independent of, a particular intervention.

Future Needs

What does the future hold for dynamic ventriculography? In addition to the need to determine optimal reference points for measuring segmental shortening, there may be a need for implementing more than the conventional biplane arrangement so that four simultaneous views, rather than the present two, are obtained. Correlations with radioisotope angiography and B-scan ultrasonography are also essential. If these procedures are shown to be accurate and reliable, it may be possible to avoid repeat cardiac catheterization in patients and to perform sequential ventriculograms noninvasively. Lastly, it is obviously necessary to employ the concept of dynamic ventriculography to study the *right* ventricle now that suitable geometrical models[23,24] have been presented.

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ATRIAL PACING DURING ANGIOGRAPHY—I*

lthough prolonged periods of ventricular ectopy or sino-trial arrest such as those reported by Desser and Benchi-ıol[1] may clearly result in potentially lethal consequences nd would undoubtedly benefit from prophylactic pacing, 're have noted no such complications in our experience and elieve this warrants further consideration.

We have reviewed the data of 47 consecutive patients 'ho underwent cardiac catheterization in order to demon-trate graft patency postoperatively. Of the 47 patients we ave excluded 14 because graft visualization was nonselec-ve, 2 because of occluded grafts and 2 who had received tropine before the study. The remaining group of 29 pa-ents is comparable in number to that of Desser and Ben-himol and was evaluated for the presence or absence of ignificant disturbances of conduction or rhythm during se-ective graft injections. The studies were performed an av-rage of 3 months postoperatively. A 1 percent solution of docaine was employed as local anesthesia. Eight patients 'ere studied by the Sones technique and the remainder 'ith use of the right Judkins catheter by way of the femo-al artery. Hypaque® 75 percent (3 to 6 cc) was given by and injection for coronary graft arteriography. The elec-'ocardiogram was monitored continuously on a Honeywell ıodel 1508-A Visirecorder, and recorded during and after ach injection on a strip chart recorder. The lead demon-rating the most definite atrial and ventricular complexes as selected for monitoring. Seven patients had an isolated 'aft to the right coronary artery and 9 an isolated graft to ıe left anterior descending artery, 11 had double bypass 'afts, 1 had a triple vessel bypass and another had four essels bypassed. A total of 40 patent grafts were studied ith an average of 3.5 injections per graft for a total of 145 lective injections.

There were only seven episodes of rhythm or conduction sturbance during these 145 injections (Table I), com-ared with 31 in 39 injections in the reported series. All ere brief and self-limited and were not believed to require ıerapy. In two patients, two of six injections into the graft the left anterior descending artery resulted in an episode sinus arrest that was one beat in duration and resolved ithout treatment. In another patient, three of six injec-ons into the graft to the left anterior descending artery re-ılted in an episode of apparent Mobitz type II block, also ıly a single beat in duration. The remainder of the injec-ons in these patients produced no complication. In the urth patient, a single ventricular premature beat was oted during each of two injections into the right coronary terial graft. These beats were well off the T wave. No sig-ficant sinus bradycardia was noted.

We are unable to explain the differences in experience tween these two groups of patients. Desser and Benchi-ol do not present their method of administration of dye, nether by power or hand injection. As noted, we employ hand injection and use somewhat less dye than used by them. It is conceivable that a larger bolus injection of dye may increase the anoxic period significantly and contribute to the greater incidence of rhythm and conduction disturbances seen in their patients. We also considered the possibility that their patients had more severe obstruction of the nongrafted vessels, which might result in a higher frequency of such complications due to the greater proportion of myocardial perfusion compromised during patent graft injection. However, we could find no such correlation in our patients.

We would be greatly interested in the results of studies from other, larger groups of patients, in view of the relatively small size of both our group and that of the authors. In view of our own experience, however, it is not presently our practice to employ pacing routinely for catheterization studies of patients after saphenous vein bypass grafting.

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*Views expressed are those of the authors and do not represent official Air Force cy.

Occurrence of Conduction or Rhythm Distrubances During Aortocoronary Graft Angiography

Arrhythmia	Graft Site RCA	LAD	Total
Sinus bradycardia or arrest	...	2	2
Sinus bradycardia + ventricular premature beats	...	...	...
Ventricular premature beats + sinus slowing, rate 60/min	...	...	...
Sinus bradycardia + A-V junctional escape rhythm	...	...	...
Advanced A-V block	...	3	3
Sinus slowing and ventricular tachycardia	...	...	...
Sinus bradycardia + ventricular tachycardia	...	...	...
Ventricular premature beats	2	...	2
Total	2	5	7

LAD = left anterior descending coronary artery; RCA = right coronary artery.

Reference

1. **Desser KB, Benchimol A:** Atrial pacing during selective aortocoronary saphenous vein bypass angiography. Am J Cardiol 34:19–22, 1974

REPLY

Descriptions of atrial pacing as a method for preventing certain untoward electrical and hemodynamic sequelae of both coronary[1] and aortocoronary graft bypass[2] angiography evoke more response than the original papers relating to the incidence of such arrhythmias during these proce-

dures.[3,4] In January 1973 we described disturbances of rate, rhythm and conduction in 19 of 20 subjects undergoing bypass graft opacification.[4] This latter paper did not result in even a single letter to the authors. On the other hand, suggestions that right heart pacing or a "standby" pacing catheter be utilized to prevent these effects appear to raise the concern of certain catheterization teams. Specific responses to the comments of Hall and Bryson are as follows:

Our study group was composed of 30 consecutive subjects with patent grafts who underwent selective saphenous bypass angiography. Hall and Bryson excluded 14 of 47 cases (30 percent) because of nonselective opacification. The absence of selective opacification in almost one third of subjects studied "in order to demonstrate graft patency" is, in our opinion, unacceptable. These figures do not lend support to the contention that the study groups were in fact comparable.

We are not supplied with information regarding other types of premedication that may have influenced their results.

Our patients received 6 to 8 ml of Hypaque®, in contrast to the 3 to 6 ml utilized by Hall and Bryson.

The statement "no significant sinus bradycardia was noted" is unclear. In our study any angiographically induced prolongation of the P-P interval to greater than 1 second was classified as sinus bradycardia.

We consider sinoatrial arrest and Mobitz type II atrioventricular (A-V) block as significant disturbances of cardiac rate and A-V conduction.

Lesser volumes of contrast medium generally result in fewer cardiac arrhythmias during selective aortocoronary graft and coronary angiography. In addition, opacification of grafts supplying vascular segments distal to a complete or near-complete coronary arterial obstruction usually results in greater electrocardiographic changes.

We assume that Hall and Bryson are confining their definition of "conduction disturbance" to atrioventricular abnormalities. Well described intraventricular conduction disturbances arising as a consequence of graft opacification[4] cannot be properly assessed by means of single electrocardiographic lead recording.

Finally, experience in performing coronary and, recently, graft angiography in over 2,000 subjects with standby or routine pacing reveals catheterization-related mortality rates that perhaps are more favorable than those cited in reports. There has been a single death during this period. In 11 subjects, it is our belief that application of the pacing technique has prevented what otherwise might have been a potentially fatal result.

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ATRIAL PACING DURING ANGIOGRAPHY—II

Desser and Benchimol[1] recently recommended the use of atrial pacing to prevent a variety of adverse electrical (and subsequently hemodynamic) abnormalities during selective aortocoronary bypass angiography. They specified that their patients did not receive atropine; no mention was made of premedication of any type.

Our experience during the last 10 years suggests that several observations are in order: (1) The importance of premedication with an anxiety-alleviating drug cannot be overestimated, particularly in men. Initial slowing of the heart rate (that is, before injection of contrast material in a coronary artery or its bypass) occurs commonly in men (±25 percent) and very rarely in women (±1 percent). Without premedication to relieve anxiety, the majority of women patients (±65 percent) will have an increased heart rate before injection of contrast material whereas approximately 25 percent of the men will have sinus bradycardia (40 to 60 beats/min). For this reason, we routinely administer a combination of morphine sulfate (1/6 gr) with atropine sulfate (1/150 gr) subcutaneously 20 minutes before the opacification of the coronary arteries or their bypass or both. (2) With the aforementioned premedication, only 3 percent of the men have a heart rate below 50/min. If, in these few men, the first injection of dye results in slowing of the heart rate below 30 beats/min for more than 2 seconds, we inject atropine sulfate (1/150 gr) intravenously and wait for 2 minutes before making the next injection.

By using these simple measures, we have been able to prevent the development of marked sinus bradycardia or arrest whereas these complications occurred commonly in patients without premedication. After 10 years, 5,000 selective coronary cinearteriograms and 300 selective bypass cineangiograms, we are still waiting to see the appearance of ventricular premature beats, advanced atrioventricular (A-V) block or ventricular tachycardia after sinus slowing or sinus arrest as reported by the authors. We are unable to state if this is due to the relief of anxiety by the premedication or to the use of a different contrast agent (Renografin® 60 or 75 as opposed to Hypaque®).

In conclusion, we believe that sinus bradycardia or sinus arrest after injection of dye into a coronary artery or its bypass can usually be prevented by relieving the patient's anxiety with adequate premedication and, in the few instances where this is not sufficient, by the additional use of a small dose of atropine intravenously.

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Reference

1. **Desser, KB, Benchimol A:** Atrial pacing during selective aortocoronary saphenous vein bypass angiography. Am J Cardiol 34:19–22, 1974

REPLY

An absence of serious cardiac arrhythmias during the course of 5,000 selective coronary cinearteriograms and 300 selective bypass graft angiograms performed by Demany and Zimmerman attests to their skill and the value of premedication before these procedures. Our patients did not receive any premedication before diagnostic and postoperative angiography. An effort to assess properly the influence of bypass grafting on left ventricular function generally precludes major pharmacologic intervention before cardiac catheterization. In the event that such study is not contemplated, either premedication or right atrial pacing suffices.

Further study will determine whether or not right atrial pacing results in lower morbidity and fewer episodes of ventricular tachycardia at normal sinus rates during catheterization as compared with atropine administered before catheterization.

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THE FOURTH HEART SOUND—A NORMAL FINDING?

In a series of publications over the past 3 years dealing with the fourth heart sound and coronary revascularization, David Spodick has been quite effective in exposing the "emperor's new clothes."[1–3] In a recent article[4] comparing the prevalence of the fourth heart sound (S_4) in normal subjects and hypertensive middle-aged men, he and his colleagues demonstrated that a fourth heart sound could be recorded in 70 percent of subjects in both groups. Spodick has previously shown that older subjects, considered to be normal, also have a prevalence rate of recordable fourth heart sounds of approximately 70 to 75 percent.[3,5] Experienced cardiologists have taken great exception to the meaning of these findings.[6–9]

Wilbert Aronow and colleagues[10,11] have also demonstrated that one can record a fourth heart sound in a significant number of normal persons, although their incidence rate is far lower than that of Spodick's normal subjects. These studies have certainly done much to make all auscultators listen more carefully, and to try to document with greater objectivity what it is we are calling fourth heart sounds. It has been aptly emphasized that in the presence of palpable presystolic distension, one is very likely to be correct in verifying an abnormal S_4,[8,9,12] and also that many times the so-called S_4 is in reality splitting of the first heart sound.[8,9,13]

The question of *audibility* versus *recordability* is crucial. This has been clearly stressed by Noble Fowler, Robert Adolph and Morton Tavel.[6–9,14] There is little doubt that low frequency vibrations of S_4 can be recorded with high quality microphones in most normal persons, as Spodick and others have demonstrated. Spodick[13] has previously shown that "blinded" observers hear S_4's with the same frequency that they are recorded but, of course, one cannot tell whether his observers were really hearing a split S_1, and calling it an S_4; there were more than 50 percent false positive responses in that study. In my experience, and that of virtually every clinical cardiologist that I know, it is most unusual to hear a *definite* fourth heart sound in middle-aged or older persons who are apparently free from cardiac disease. We occasionally hear what we think is an S_4 in a "normal" subject, but nowhere near the reported incidence rate of 70 to 75 percent.[3–5] Spodick deplores matching one's "experience" over "an appropriately designed study,"[15] but serious questions have been raised about the design of his "blinded" study.[9]

Spodick himself has inadvertently weakened his position in a recent study from his group demonstrating that chronic alcoholics have abnormal systolic time intervals, thus indicating subclinical myocardial dysfunction.[16] That study, in conjunction with several other recent investigations,[17–19] clearly indicates that acute and chronic alcoholism is frequently associated with impaired myocardial function, even when there are no symptoms or signs of cardiac disease. In the study of Spodick et al.,[16] 26 normal control subjects and 26 ambulatory chronic alcoholics clinically free from heart disease were carefully evaluated by systolic time intervals. The mean age in both groups was approximately 45 years; thus many of these persons are in the same age group as in Spodick's recent publication.[4] The group of chronic alcoholics clearly had abnormal systolic time intervals, with prolonged preejection periods, and decreased left ventricular ejection times, highly suggestive of latent cardiac malfunction; *apparently, however, normal fourth heart sounds or "atrial gallops" were not heard.* "All subjects—both alcoholic patients and screening-clinic normal persons—were free of heart abnormality .... there were no murmurs or abnormal heart sounds ...."[16] Two of the authors, Spodick and Pigott, participated in the phonocardiographic studies in normal subjects,[3,5,13] and must have been well aware of the importance of listening for a fourth heart sound.

The best explanation for the marked discrepancy in hearing an S_4 in Spodick's two studies,[13,16] is that fourth heart sounds were simply *inaudible* in the study of alcoholics. Presumably, the middle-aged control subjects and alcoholics would have had a 70 to 75 percent incidence rate of fourth heart sounds *recordable* with specialized recording equipment. The high incidence rate of false positive S_4's (56 percent) in his "blinded" study[13] makes it even more apparent that auscultator expectation and experience of the auscultator play a large but poorly defined role in this controversy.

While the arguments are sure to continue, it is important to emphasize that auscultation of a *definite* atrial sound in a middle-aged or older person is not likely to be a normal event, in the experience of many practicing cardiologists.[6,8,20,21] On the contrary, there are considerable data to substantiate the view that an *audible* fourth heart sound is, in fact, an indication of decreased left ventricular compliance, if not a definite elevation of left ventricular diastolic pressure,[12,21,22] and is not simply a hallmark of aging.

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REPLY: THE FOURTH HEART SOUND: AN INADEQUATELY INVESTIGATED SUBJECT

The S_4 problem is a specific case of a more general question: unexamined acceptance of traditional wisdom. I am grateful to Abrams for the opportunity to continue the dialogue on significance of fourth heart sounds. In citing our work, he has read widely but not always deeply. While acknowledging the validity of particular disagreements (especially some paraphrasing Tavel[1]), I deplore the attempt to make certain points by selective citations, and by posing questions about our work that we ourselves have repeatedly raised.

Abrams' assertion that "many times the so-called S_4 is in reality splitting of the first heart sound" is a reasonable auscultatory generalization, but has he investigated this—that is, *how many* times? Moreover, he ignores the reverse possibility: How many times is a so-called split S_1 "in reality" an S_4? How do we decide which is "in reality" which? Indeed, his reference 13 on this point does not support his reasoning since that reference was our report,[2] which concludes that "false audibility (of S_4) was *not* related to the low-frequency component of S_1 or to split S_1." In fact, that was so precisely among our 56 percent of subjects with false positive results. This figure is only apparently a bad result, since it is a fraction of the small total without a recordable S_4. It represents only 19 of 122 patients. Curiously, Abrams omits the 25 *false negative* results. Yet, the false positive results weakened our auscultators' performance, possibly because of zealous belief in "S_4"—the exact counterpart of supplying nonexistent "split S_1" because of zeal for the traditional belief. In this context, Abrams correctly cites "auscultator expectation." But in the absence of investigations designed to minimize biases, this factor cuts two ways. For example, "auscultator expectation" held for many years that the second heart sounds were unitary events with "A_2" and "P_2" on respective sides of the upper sternum. Generations of physicians and voluminous studies reported them in this way. Now we hear and report S_2 as a binary event in terms of its splitting dynamics. *We are listening to the same sound, but now we hear it differently.* Similarly, the conventional wisdom regarding "split S_1" might also provide a misleading "auscultatory expectation." To the extent that our studies prove to be flawed, I will be equally guilty.

Our studies have not yet provoked formal reinvestigation of S_4. Although our phonocardiographic results by themselves must be totally objective *for the equipment used* (that is, we recorded undeniable S_4's in normal subjects and patients), the crucial question of auscultation remains. Our auscultatory study, while electronically simplistic (and currently the subject of an improved protocol), utilized the only "scoring system" possible in clinical cardiology—the phonocardiogram. We recognize that it is impossible at present to determine exactly which vibrations are audible in a train of vibrations occurring within milliseconds of each other, such as the $S_4 + S_1$, (o-a-b-c) complex,[7] among which we usually hear only two discrete sounds. Intricate questions of frequency-audibility thresholds, masking and reverse masking are involved. Moreover, the logarithmic response of the ear to pure audiometric tones may not have a direct counterpart in the vibratory complexities of actual heart sounds. These formidable obstacles confront us, but they confront our critics equally. We attempted to minimize them by elaborate blinding procedures—admittedly imperfect, but aimed at reducing those biases inherent in preliminary knowledge of patients' clinical data and prejudices inherent in the traditional but unexamined concepts of S_4.

Abrams cites the work of Bethell and Nixon (his reference 12) to substantiate the view that an audible S_4 is ipso facto abnormal. Curiously, he omits the same authors' citation of work by us and others substantiating an age-related increased incidence of S_4 and including their statement that "it may be a physiological event in *many* cases" [3] (my emphasis). He further cites Fowler, Adolph and Tavel as stressing "the question of *audibility* versus *recordability.*" He does not cite the very paper by us that precipitated his letter, which states: "Registration by phonocardiogram does not prove its audibility." Also not cited was our own extensive section raising caveats and questions about our own work (Abrams' reference 5), in which we declare: "The audibility study served to raise more questions about current concepts of S_4 than it answered . . . . We believe it has not completely settled any of these issues . . . . It would be desirable to have confirmation or refutation by other controlled studies . . . . since the results of auscultation for a frequently subtle phenomenon remain highly subjective." [5]

Abrams states that I have "inadvertently weakened" my position on S_4 in our report of preclinical cardiac malfunction in apparently normal alcoholics.[6] He deduces that, despite poor functional indexes in the alcoholics, *"normal fourth heart sounds or atrial gallops were not heard"* (his emphasis). He has no evidence for this. Actually they were disregarded. I have always considered abnormal any palpable and subjectively loud S_4.[2,4,5,7] In the alcoholic study any subjectively loud atrial sounds thus had to be excluded. Indeed, since our S_4 studies point to the mere presence of S_4 as possibly physiologic, the question could not properly arise either by auscultation or by phonocardiography. It could only have arisen if we shared the traditional view of S_4. Moreover, since we cannot yet tell the pathologic from the nonpathologic, we could not consider *any* recorded S_4. Thus we did maintain fidelity to our S_4 results, and it is Abrams who falls victim to his own view. Finally, this was a systolic interval study and here Abrams also overlooked Table I of our auscultatory study,[2] which showed a group trend toward better values for systolic intervals in all those with S_4 by phonocardiogram.

In conclusion, let me acknowledge again that our investigations have been at best imperfect and at worst invalid. But we tackled the S_4 problem by attempting to minimize subjective and objective bias. Examination of our illustrations[2,4,5] will show that the phonocardiographic prevalence of S_4 cannot be denied—at least using Maas and Weber filters (discussed elsewhere[8]). Our results with Hewlett-Packard filters do conform more closely to those of most others.[8] Which phonocardiographic result is "right"? Which auscultatory result is "right"? This remains a problem in observer performance. In a meticulous investigation, observer performance among experienced auscultators varied astonishingly when they were "blinded" to everything else about the patient.[9] Who among them was "right"? The problem must be dealt with by appropriately designed studies.

Evaluation of S_4 is more complex than the recently cor-

rected traditional concept of S_2 and its components, but it is best to approach each question in search of Truth rather than to attempt to reconfirm Established Belief. (Much early phonocardiographic equipment was designed to do just that.) Goethe observed: "What we know, we see," and Will Rogers provided the corollary: "It isn't what we know that causes trouble, it's what we know that ain't so."

Addendum: Since this letter was submitted, Tavel has reported a phonocardiographic prevalence of S_4 in patients over 40 identical to ours in the paper criticized by Abrams: "Fourth heart sounds were recorded in 71 percent (11 of 14) of normal controls" (catheterized to compare with patients with aortic stenosis, 85 percent of whom had S_4) (Tavel et al: *Circulation* 50: Suppl III: 247, 1974).

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AMIODARONE HYDROCHLORIDE

In answer to several inquiries concerning our article,[1] amiodarone hydrochloride was originally developed by S. A. Labaz N.V. from Brussels, Belgium. In Argentina, the drug is manufactured under the name Atlansil by Laboratorios Roemmers S.A., Buenos Aires, Argentina.

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Reference

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P-R INTERVAL IN BIFASCICULAR BLOCK

Levites and Haft[1] have concluded that the P-R interval is probably of some help clinically in separating normal from abnormal intraventricular conduction time in patients with right bundle branch block and left axis deviation; that it is not useful as an indicator in patients with left bundle branch block or right bundle branch block with right axis deviation; and that His bundle electrography is necessary in this latter group to detect H-V prolongation.

However, they have failed to emphasize the most obvious conclusion in their observations of the P-R interval with bifascicular block; that is, the length of the P-R interval accurately differentiates between normal and abnormal atrioventricular (A-V) nodal conduction time. In their 41 cases with a P-R interval of 200 msec or less, the A-H interval was normal (less than 130 msec) in 40. In their 22 cases with a P-R interval of 210 msec or greater, the A-H interval was abnormal (greater than 130 msec) in 20.

Thus, the P-R interval can be used as a valid indicator of the conduction time in the A-V node, but is probably of little value in predicting normal or abnormal intraventricular conduction time in patients with bifascicular block. His bundle electrography is essential for this measurement.

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Reference

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PREDICTIVE VALUE OF LABORATORY TESTS

The precise use of terms is essential if we are to communicate effectively within and between scientific disciplines. Two of the most commonly confused terms in medicine today are sensitivity and specificity. It is regrettable that Schweitzer et al.[1] used these terms incorrectly. Shown is their Table I defining these terms followed by a table with the correct definitions.

Sensitivity, specificity, predictive value and efficiency define the accuracy of a laboratory test. Sensitivity indicates the frequency of positive test results in patients with a particular disease, whereas specificity indicates the frequency of negative test results in patients without that disease. The predictive value of a positive test result indicates the percent of patients with disease among all patients with positive test results. The predictive value of a negative test result indicates the percent of patients without disease among all patients with negative test results. The efficiency of a test indicates the percent of patients correctly classified (as having or not having disease) by the test (Table II). False positive results are therefore calculated as 100 percent − predictive value of the positive test. If a test has a predictive value (positive) of 90 percent, then 90 percent of the positive results are true positive results and 10 percent are false positive results.

In diagnosis we are most interested in the predictive value of the positive result. These are patients who are presumed to have a particular disease and undergo further di-

TABLE I

Sensitivity and Specificity of Exercise Criteria

Results of Exercise Test	Results of Coronary Angiography	
	CAD	NCAD
Positive	A	B
Negative	C	D

Sensitivity of exercise criterion = A/(A + C) expressed as percent.

Specificity of exercise criterion = A/(A + B) expressed as percent.

Thus, false positive results = 100 − specificity; false negative results = 100 − sensitivity.

Reproduced from Schweitzer et al.[1]
CAD = coronary artery disease; NCAD = no or insignificant coronary artery disease.

agnostic tests. Of this group, those patients who do not have the disease will be defined as false positives. In the discussion that follows, predictive value will be used to refer to the predictive value of the positive test result. *A marked change in predictive value occurs when there is a change in the prevalence of the disease in the population under study.* For example, we could know from a test's sensitivity and specificity that it was positive in 95 percent of patients with a disease and negative in 95 percent of patients without a disease. Table III shows the change in predictive value that occurs for this test with changing prevalence of disease. It can readily be seen that a particular test has an increased predictive value when the disease occurs with a greater prevalence. This explains why a good diagnostic test frequently fails as a screening test, when the decrease in prevalence is quite marked. When clinical judgment is used in ordering laboratory tests, the patient suspected of having a particular disease is placed in a new population with a high rate of prevalence or probability of disease. Therefore the test performs much better.

Figure 1 illustrates how sensitivity and specificity are altered by the selection of an upper limit of normal for a particular test. If patients admitted to the coronary care unit with the diagnosis "rule out myocardial infarction" were divided into those with and those without myocardial infarction on the basis of history and electrocardiographic findings and then if the enzyme results for each group were expressed as a frequency distribution, the classic overlapping distributions seen in Figure 1 would be seen. It is impossible to select a cutoff point for enzyme activity that would afford complete discrimination between the two groups. At any cutoff point, one must sacrifice sensitivity for specificity and vice versa. Herein lies the major flaw of laboratory diagnosis: The tests are not sensitive and specific at the same time. Muliple laboratory tests improve the predictive value somewhat, but the trade-off between sensitivity and specificity always remains. If we wanted to select a cutoff point for the test illustrated in Figure 1, any point in the overlapping region would do. Table IV lists several cutoff points with the sensitivity, specificity and predictive value associated with each.

Rather than use the term cutoff point or upper limit of normal, we refer to this point of reference as the referent value. For any laboratory test studied in any disease, the predictive value of the test in diagnosing the disease can be calculated at any referent value.

This model[2] is clearly not restricted to laboratory testing although it has been applied extensively in clinical pathology.[3–8] It is applicable in radiology and cardiology as well. In fact, applications in cardiology using this model and the

TABLE II

True Diagnosis

Test Result	With Disease	Without Disease	Total
Positive	A	B	A + B
Negative	C	D	C + D
Total	A + C	B + D	A + B + C + D

Sensitivity (positive test results in patients with a particular disease) = $\frac{A}{(A + C)} \times 100$ expressed as percent.

Specificity (negative test results in patients who do not have a particular disease) = $\frac{D}{(B + D)} \times 100$ expressed as percent.

Predictive value of a positive test (percent of patients with positive test results who have a disease) = $A/(A + B) \times 100$.

Predictive value of a negative test (percent of patients with negative test results who do not have a disease) = $D/(C + D) \times 100$.

Efficiency of test (percent of patients correctly classified as having or not having a disease) = $\frac{A + D}{A + B + C + D} \times 100$.

A = true positive, the number of patients with a disease correctly classified by the test; B = false positive, the number of patients who do not have a disease misclassified by the test; C = false negative, the number of patients who do not have a disease misclassified by the test; D = true negative, the number of patients who do not have a disease correctly classified by the test.

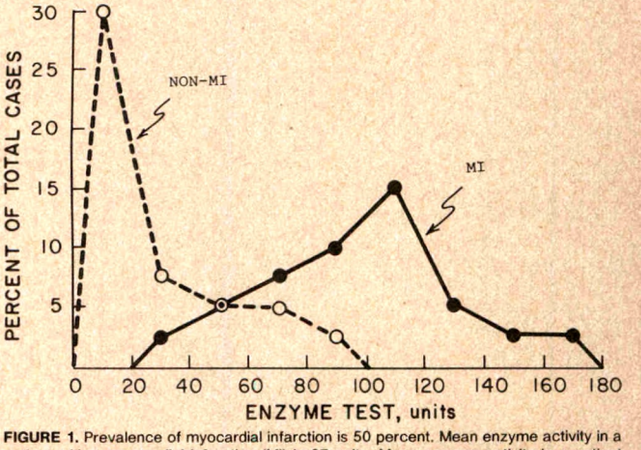

FIGURE 1. Prevalence of myocardial infarction is 50 percent. Mean enzyme activity in a patient with a myocardial infarction (MI) is 97 units. Mean enzyme activity in a patient who has not had a myocardial infarction (non-MI) is 27 units. Upper limit of normal is 20; sensitivity is 100 percent, specificity is 60 percent. Upper limit of normal is 100; sensitivity is 50 percent, specificity is 100 percent.

TABLE III

Predictive Value as a Function of Disease Prevalence*

Prevalence of Disease (%)	Predictive Value (%)
1	16.1
2	27.9
5	50.0
10	67.9
15	77.0
20	82.6
25	86.4
50	95.0

* For laboratory test with 95 percent sensitivity and 95 percent specificity.

TABLE IV

Enzyme Test

Referent Value (cutoff point)	Sensitivity (%)	Specificity (%)	Predictive Value (%)
20	100	60	71.4
40	95	75	79.2
60	85	85	85.0
80	70	95	93.3
100	50	100	100.0

Disease prevalence = 50 percent.
Referent values and associated predictive values for this test are illustrated in Figure 1.

definitions reviewed in this letter have already been reported.[9,10]

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J POINT DEPRESSION IN THE EXERCISE ELECTROCARDIOGRAM

The correlative method of presentation in the article by Kattus[1] surely must be viewed as excellent teaching. Those of us in exercise physiology are indebted to Dr. Kattus for his leadership in this field. However, I must quibble with his lack of true scientific approach to the problem of J point depression, which he stated is "often a stage in the development of the ischemic response." This is a classic example of the "post-hoc" fallacy.

I would have appreciated his stating that this is his bias on what may turn out to be a clinical fact but is not yet firmly established. However, his statement on the significance of J point depression with no qualification other than "often" now exists in the literature. While this kind of prejudicial statement could be entirely true, the statistically significant evidence was not quoted and is lacking as far as I am aware.[2] Kattus' statement will be quoted henceforth and without the "often." Patients will be found to have coronary disease on the basis of a normal upsloping J point depression when indeed they have no coronary disease at all.

Figures of such stature as Kattus must be careful to make clear when they are moving from verified scientific data into the realm of impressions. Obviously it is my bias that J point depression may be and usually is entirely normal and that as yet there are no well accepted statistically valid criteria to differentiate normal from abnormal J point depression. I would appreciate anything Dr. Kattus has to offer concerning these criteria as well as clarification of his statement.

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REPLY

In reply to Dr. Silverstein's scolding about not being scientific enough in my comments about the significance of J point depression in the exercise electrocardiogram, the article was not meant to be a rigorously designed scientific treatise, but rather an essay in which I sought to share experience with the reader. I tried to point out simply that the appearance of J point depression cannot always be taken as an innocent finding. At times it is the only detectable electrocardiographic change during true anginal pain.

I readily accept that this change is frequently encountered in normal, healthy and well conditioned persons. I don't know how to distinguish the innocent J point depression from the bad except to look for corroborative evidence of myocardial ischemia such as chest pain or abnormal coronary angiographic findings. I indicated that we are trying to devise a test to see if administration of nitroglycerin will selectively reverse the J point depression of true ischemia and perhaps help to differentiate the innocent from the bad. We, too, would like to know how to be sure about this point.

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EARLY HOSPITAL DISCHARGE AFTER MYOCARDIAL INFARCTION

In their study of early mobilization after myocardial infarction Bloch et al.[1] referred to a paper by us[2] pertaining to early discharge after acute myocardial infarction: "However, since only 15 percent of the patients hospitalized for infarction were admitted to their study, the applicability of their conclusions is severely limited." We should like to take exception to this statement and make the following comments.

Although it is true that only 15 percent of the 925 consecutive patients with definite myocardial infarction screened by us were admitted to the study, the absolute number of patients in both series is similar (138 in ours, 154 in theirs). The reasons for exclusion in our study should be examined more carefully. Twelve percent died before assessment for randomization; an additional 18 percent with pump failure on the 5th hospital day and 8 percent with heart block reflect the somewhat skewed nature of patients with myocardial infarction referred to our institution because of our particular interest in the treatment of pump failure. A further 8 percent were excluded because of complicating medical illness necessitating a longer stay, and 7 percent were rejected for "social" reasons. Thus there is good reason to believe that many more patients would be eligible in most hospitals where more "typical" cases of myocardial infarction are seen.

We studied the problem of early discharge as well as early mobilization by randomly assigning our patients to two groups, one discharged at 2 weeks and the other at 3 weeks, and found no difference in subsequent outcome between the two groups. The average length of stay of the early mobilization group of Bloch et al., 21.3 days, corresponds to that of the "long stay" group in our study.

The point is that most patients with uncomplicated acute myocardial infarction are candidates not only for early mobilization, but also for early discharge. Most can be

discharged at 2 weeks, and there is little justification for keeping them longer than 3 weeks.

The importance of both our paper and that of Bloch et al. is that, despite the fact that several studies of early mobilization and discharge have been reported, these are the only two that are truly randomized.

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REPLY

The study by Hutter et al. is an important randomized study. Our comment about their report was directed at the low proportion of all cases with acute myocardial infarction included (15 vs. 75 percent in our study).

The mortality rate before randomization was about the same in the two series. In our study, patients were not excluded because of medical illness necessitating a longer stay, thus lengthening somewhat the average hospital stay of the early mobilization group. The principal difference in the material of the two studies is the percentage of patients excluded because of complicated myocardial infarction (50 percent in the Hutter study vs. 15 percent in our study). This difference is partly related to the skewed nature of patients referred to the cardiac unit of the Massachusetts General Hospital, and partly due to the fact that the Geneva definition of uncomplicated infarction was far less restrictive. In addition, in Hutter's study patients were randomly assigned into groups on the 6th hospital day, after exclusion of patients with ventricular fibrillation, ventricular tachycardia, asystole, second degree heart block or complete heart block; persistence of more than five ventricular premature beats per minute, multifocal ventricular premature beats or paired ventricular premature beats into the 5th day; continued requirement of any antiarrhythmic therapy into the 5th day; persistence of any evidence of congestive heart failure into the 5th day; any hypotension requiring vasopressor agents; definite thromboembolic complications during the first 5 days; coronary pain persisting into the 5th day; occurrence of any acute episodes of infarction within the preceding 6 months. In contrast, in our study patients were randomly assigned into groups 24 to 48 hours after admission, and the only causes of exclusion were severe heart failure, cardiogenic shock, severe rhythm disturbances, severe thoracic pain or severe psychological problems.

The study of Hutter et al. showed the benefit of early mobilization and early discharge after uncomplicated myocardial infarction. We demonstrated that this practice can be applied to the majority of patients admitted for myocardial infarction in a nonreferral general hospital.

Finally, we suspect that both of our reports overemphasized somewhat the absence of statistically significant differences. However, due to relatively small sample size and number of events, the statistical power was not sufficient to establish that there were absolutely no differences. But the thrust of these two truly randomized studies is that well-planned early mobilization is now unequivocally demonstrated to accomplish considerable benefits without excessive risks.

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METHYLPREDNISOLONE IN ACUTE MYOCARDIAL INFARCTION

The study by Vyden et al.[1] requires some clarification. It appears from the experimental protocol that the authors are treating not simple acute myocardial infarction, but cardiogenic shock (systolic blood pressure below 80 mm Hg, sustained for 30 minutes).[2] In their preparation, mean systemic vascular resistance was increased concomitantly with the drop in cardiac index. In this condition, it has long been known that glucocorticosteroids reduce peripheral vasoconstriction, thereby increasing the stroke volume of the left ventricle.[3,4]

In myocardial infarction without shock, methylprednisolone has not produced any hemodynamic changes.[5] Thus, the beneficial effect of glucocorticosteroids in acute myocardial infarction must be advocated on a basis other than hemodynamic, and the beneficial hemodynamic effects seen in these experiments probably cannot be extrapolated to the human situation for the reasons the authors themselves enumerate.

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REPLY

Feola states that "mean systemic vascular resistance was increased concomitantly with the drop in cardiac index" when acute myocardial infarction was produced in our preparation and draws certain conclusions from this. However, mean systemic vascular resistance was not significantly increased with the production of infarction, changing from 5.71 ± 0.46 to 6.88 ± 0.76 ($t = 1.41$), and thus the conclusions drawn are not valid.

Most clinicians treating acute myocardial infarction would agree cardiogenic shock is accompanied by a marked fall in stroke work index coupled with a significant increase to abnormal levels in left ventricular end-diastolic pressure. However, in our preparation there was no change in left ventricular end-diastolic pressure of any significance

and therefore the criteria of true cardiogenic shock were probably not met. However, the degree of acute myocardial infarction induced was severe, as shown by the fall in stroke work index.

Our findings agree with the study performed by Spath et al. in that at 30 minutes (the only period of time at which the two studies can be compared) methylprednisolone sodium succinate has no effect on total systemic vascular resistance and no systemic vasodilatation has occurred. In our study we examined each of the regional circulations, a study not performed by Spath et al., and found that the coronary circulation (which received only a small proportion of total cardiac output and is therefore not likely to be accurately reflected in total systemic hemodynamic measurements) improves, as seen by the increase in mean coronary vascular blood flow, the drop in mean coronary vascular resistance and the narrowing of the arteriovenous (A-V) oxygen difference across the coronary bed (see Fig. 7 and Table I in our study).

In a more recent study, Masters et al.[1] concluded that methylprednisolone sodium succinate appears to improve collateral blood flow into the infarcted area with a significant improvement in metabolism, thus supporting some of our results. However, we agree with Feola that corticosteroids probably benefit the infarcted heart from other mechanisms, in addition to any hemodynamic benefit, as stated in our study.

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POLARIZING SOLUTIONS

We have emphasized several times that polarizing treatment is not the same as infusion of glucose-potassium-insulin solution.[1,2] If this solution is not properly given it will have a depolarizing effect during diastole instead of repolarizing the muscle fibers, which is the first step in polarizing treatment. The report of Gould et al.[3] is an example of what should not be done to improve cardiac metabolism.

Evidently the authors have not grasped the concept of polarizing treatment and it is suggested they study our book[4] wherein polarizing treatment is defined. They must know that infusing the polarizing solution in 10 minutes (in some cases in 8 minutes) will increase interstitial potassium (Ke^+), consequently decreasing the ratio Ki^+/Ke^+, that is, increase conduction delay and depolarization of the cell instead of polarization). They looked for a good polarizing effect in 10 minutes, but days, weeks and even months are needed to obtain a permanent polarizing effect.[2]

The authors used a different technique from that we have recommended to effect polarization in patients.[1,2] Have they performed experiments in animals to demonstrate the benefit of the solution they administered to their patients, as we did for many years to demonstrate that our technique was beneficial and safe for use in man?

Gould et al. are undoubtedly delaying the benefits that cardiac patients can obtain[5] from polarizing treatment with use of the technique we have recommended.

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REPLY

We are well aware that various workers have used different concentrations and various time periods in administering the polarizing solutions. This may lead to different clinical results. However, it was not our intention to duplicate the exact schedule suggested by Sodi-Pallares et al. We demonstrated that potassium administration can impair conduction through the atrioventricular (A-V) node. Further greater quantities of potassium can produce delays in the His-Purkinje system, as reflected by a prolongation of the H-Q interval.[1] Thus potassium, either in the polarizing solution or administered by itself, can be potentially hazardous. Ettinger et al.[2] have recently infused potassium in 30 dogs while performing serial His bundle electrograms. They also observed that the sequential changes included A-V junctional delays and block, followed by acceleration of junctional pacemakers and conduction delays in the ventricular specialized tissue and ventricular muscle.

Perhaps glucose and insulin without potassium protect the jeopardized myocardium without producing conduction delays. This possibility is certainly worthy of further investigation. Maroko et al.[3] have shown that even glucose solutions can exert a protective effect against myocardial ischemia in the presence of experimental coronary occlusion.

It was not our desire to destroy the concept of the polarizing solutions. However, as additional information becomes available, modification of the concept may be desirable.

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VASODILATOR AGENTS

Vasodilators.. Judge TG. **Practitioner** 213(1276 SPEC NO):467-9, Oct 74 (14 ref.)

BOOK REVIEWS

CARDIOGENIC SHOCK, MECHANISM AND MANAGEMENT by Richard J. Kones, MD, Mt. Kisco, New York, Futura Publishing, 1974, 386 pages

Despite careful monitoring and pharmacologic management, the high mortality rate of cardiogenic shock has continued to plague the practicing physician. Even with close supervision, its insidious onset is often overlooked. Previous reviews have shown that management of cardiogenic shock has frequently been rather stereotyped and often inadequate. Dr. Kones has written a comprehensive monograph on a timely subject that requires careful reading. The text commences with a detailed analysis of the pathophysiology of cardiogenic shock. An extensive bibliography, which characterizes much of the text, freely draws on the wide experience of many researchers in the field without jeopardizing continuity of thought. The diagrams are clear and easily understood. After chapters on myocardial mechanics and myocardial oxygen consumption, the second half of the text concerns the management of cardiogenic shock. Each step in the clinical approach to the problem is backed by scientific physiologic data. The well known inadequacy of the central venous pressure, the attributes of the Swan-Ganz catheter and the less well known limitation of the pulmonary wedge pressure as measures of left ventricular end-diastolic pressure are succinctly analyzed. The chapter on catecholamines and cyclic adenosine monophosphate includes an up-to-date analysis of dopamine and is as complete as any pharmacologic text. Separate chapters on corticosteroids, digitalis and glucagon are followed by chapters on devices for mechanical circulatory assistance. An unbiased and scientific attitude prevails without use of personal anecdotes. Some recent therapeutic measures, including nitroprusside combined with mechanical assistance to combine a reduced afterload with diastolic augmentation, are unfortunately omitted. Despite the newer drugs and gadgetry that may soon appear on the horizon, this text will still remain an excellent reference for understanding the basic concepts essential for successful management of cardiogenic shock. As noted by Dr. Alfred Soffer in the foreword, Dr. Kones has demonstrated a profound gift for describing in depth fundamental areas of cardiovascular function and disease.

Mark G. Cohen, MD, FACC
Wilmington, Delaware

PROGRESS IN CARDIOLOGY, edited by Paul N. Yu and John F. Goodwin. Philadelphia, Lea & Febiger, 1974, 349 pages, $17.50

The third volume of Progress in Cardiology maintains the same standard of excellence established by the preceding volumes. Each of its 12 chapters is an essay on a timely topic in cardiology by an internationally renowned authority. The topics are thoroughly reviewed and excellently written. Although there are stylistic variations from chapter to chapter, they are not distracting and give the book its personality.

Although I enjoyed the whole book, several chapters are noteworthy: Henry Blackburn's review of the epidemiology of coronary heart disease provides a critical evaluation of risk factors written with wit and whimsy. Thomas James' review of cardiac electrical impulse conduction is extraordinarily thorough and contains an excellent bibliography. Leo Schamroth's presentation of a unified concept of ventricular arrhythmias is very provocative. Doctors Shah and Gramiak provide an excellent, well illustrated review of the clinical uses of echocardiography.

Other topics discussed include exercise cardiology, early phase of acute myocardial infarction, the role of renin-angiotensin in the pathogenesis of hypertension, the Eisenmenger syndrome, evaluation of drugs affecting the heart, current aspects of valve replacement, therapy for prevention of thrombosis and measurement of lung water. This is an excellent reference book that every internist and cardiologist will want to read and read again. It is highly recommended.

Marvin I. Dunn, MD, FACC
Kansas City, Kansas

THE HEART, edited by J. Edwards, M. Lev and M. R. Abell. Baltimore, Williams & Wilkins, 1974, 357 pages, $21.50

The Heart comprises 17 chapters, each corresponding to a lecture given as a part of the Long Course of the 62nd Annual Meeting of the United States—Canadian Division of the International Academy of Pathology that was entitled The Pathophysiology and Anatomy of the Heart. This multiple author review contains several comprehensive and elegantly written sections, and a larger number of chapters that are too brief and superficial to cover their subject matter adequately. The chapter on aortic valve disease is highly recommended to both clinicians and pathologists for its detailed and well organized clinical-anatomic correlations. In comparison, the preceding chapter on acute and chronic atrioventricular valve disease contains fewer details and is less informative.

Some chapters include clinical-anatomic correlations whereas others are limited solely to anatomy or pathology. The author of the chapter on cyanotic congenital heart disease specifically states that his presentation is oversimplified and directed to pathologists. The chapter on left to right shunts, although lucidly written, is excessively brief and limited almost exclusively to considerations of cardiac anatomy. In contrast, the chapter on pulmonary hypertension reviews clearly, and in adequate detail, normal and abnormal pulmonary vascular anatomy and pathophysiology. The chapter on anomalies of the aortic arch system is written succinctly with clear and instructive diagrams and photographs of post-mortem specimens.

In summary, my concern is not solely that this book contains a paucity of clinical and anatomic integration, but also that several chapters are too limited in scope or detail to make the book a valuable reference.

George K. Massing, MD
Birmingham, Alabama

TREATMENT OF CARDIAC EMERGENCIES, edited by Emanuel Goldberger, MD. St. Louis, CV Mosby, 1974, 353 pages, $14.00

This soft-cover text on cardiac emergencies and their diagnosis and management covers the spectrum of arrhythmias, cardiac arrest and shock, acute pulmonary edema, hypertensive crisis and syncope. A separate chapter on acute dissecting aneurysms of the aorta by Myron Wheat, Jr. is the only section not written by Goldberger.

Part II discusses the cardiac emergency equipment that is used in pacing, defibrillation and cardioversion and the various monitoring devices. The final section discusses, in logical alphabetic order, the drugs used for cardiac emergencies, their indications, toxicity and interaction.

The obvious intent of the book is to provide a pragmatic approach to cardiac emergencies rather than a comprehensive treatise on the pathophysiology or differential diagnosis of the acute cardiac conditions. Although Goldberger's personal clinical judgments permeate every chapter, his observations and conclusions are corroborated by excellent recent references.

The section on myocardial infarction includes a description of electrocardiographic localization of infarction patterns that appeared to be outside the sphere of this text and superfluous.

The chapter on the surgical management of aortic dissection, succinctly treated by Wheat, stands isolated in the coverage of surgical cardiac emergencies. Apparently, other acute surgical problems such as emergency coronary bypass, aortic bacterial endocarditis with congestive failure and papillary muscle rupture were not considered appropriate for inclusion.

The section on demand pacing and methodology is excellent, although a description of pacemaker-induced tachyarrhythmias with illustrations would have been a welcome addition. Although implying its limitations, the chapter on cardiogenic shock places excessive emphasis on central venous pressure monitoring, whereas the established value of pulmonary arterial wedge and end-diastolic pressures is given limited space in small print. Although this was an admirable intent to be concise, it appeared as an editorial afterthought.

The book is ideally suited and recommended as an easy reference for the resident, general physician and internist, as well as personnel in any emergency or intensive care unit. The clinical cardiologist may find it well suited for organizing his lectures to students and residents.

Mark G. Cohen, MD, FACC
Wilmington, Delaware

VASCULAR DISORDERS OF THE EXTREMITIES, second edition, by David I. Abramson, MD. Hagerstown, Maryland, Harper & Row, 1974, 898 pages, $42.50

In the nearly 20 years since the first edition of this text was published, many advances have been made in the diagnosis and management of peripheral disorders, and the current edition updates these features in a very commendable manner.

The text is divided into five major sections discussing the differential diagnosis of signs and symptoms of vascular disorders in the extremities, specific disorders affecting the arterial system, primary disorders of the venous system, injuries to the vascular system and a miscellaneous section including disorders of the lymphatics and vascular anomalies. The coverage of these subjects is quite thorough, the illustrations are thoughtfully selected and well reproduced.

The author joins those who regard thromboangiitis obliterans (Buerger's disease) as a specific clinical entity and places appropriate emphasis upon the histopathologic features of the disorder. The bibliographies at the end of each chapter are well selected and updated to include the most recent contributions in the field.

This extensive work on peripheral vascular disease is quite thorough, easily read and authoritative. It can be recommended to all as a reference source for vascular disorders of the extremities.

David C. Sabiston, Jr., MD, FACC
Durham, North Carolina

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

1975

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

NOV. 6–8 — **Core Curriculum: Phonocardiography and Pulse Recording—Workshop.** Morton E. Tavel, FACC, director. The Methodist Hospital Graduate Medical Center, Indianapolis, Ind.

NOV. 12–14 — **Core Curriculum: Echocardiography, Phonocardiography and Pulse Tracings—A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

DEC. 7–9 — **Advances in Heart Disease 1976.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, Calif.

DEC. 7–10 — **Structure—Function Correlations in Cardiovascular Disease.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, Va.

DEC. 10 — **Colloquia in Cardiology—Number 8: Stress and the Heart: The Influence and Management of Stress in Heart Disease.** Robert W. Oblath, FACC and Ronald Danzig, FACC, directors. Ambassador Hotel, Los Angeles, Calif.

DEC. 12–14 — **The Dwight E. Harken Symposium: Advances in the Prophylaxis and Therapy of Cardiovascular Disease.** Henry I. Russek, FACC, director. Americana Hotel, New York, N.Y.

1976

JAN. 11–13 — **Future Directions in the Management of Cardiac Disease: A Bicentennial Viewpoint.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC and James S. Forrester, co-directors. Snowmass-at-Aspen, Aspen, Colo.

JAN. 19–22 — **Core Curriculum: Pediatric Echocardiography.** Richard A. Meyer, director and Samuel Kaplan, FACC, co-director. Children's Hospital, Cincinnati, Ohio

FEB. 23–26 — **Twenty-fifth Annual Scientific Session.** Charles Fisch, FACC, president. Marriott Motor Hotel, New Orleans, La.

MAR. 11–13 — **Cardiovascular Disease—1976: Practical Diagnosis and Management.** John Ross, Jr., FACC, Robert A. O'Rourke, FACC, Joel S. Karliner, FACC and Kirk L. Peterson, FACC, directors. La Costa Resort Hotel and Spa, San Diego, Calif.

Dr. Charles Fisch, College President, is pleased to announce that the following individuals have accepted pro tempore appointments as College Governors for their respective areas:

Atlantic Provinces (Newfoundland, Nova Scotia, New Brunswick, Prince Edward Island)
Lawrence K. Harris, MD, FACC, Nova Scotia

Wyoming
Robert J. Davis, II, MD, FACC, Cheyenne

NEW MEMBERS

The following individuals were elected to membership in the American College of Cardiology on July 28, 1975, in the category indicated.

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AVINGTON, M. David, MD, West Virginia
BABITT, Henry I., MD, Maryland
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BLOOMFIELD, Dennis A., MD, New York
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STEUDEL, Wolfgang T., MD, Colorado
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† WHITE, Thomas R., MD, Indiana

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CERDA-HINOJOSA, Guillermo, MD, Mexico
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* Elected December 30, 1974
† Elected May 22, 1975

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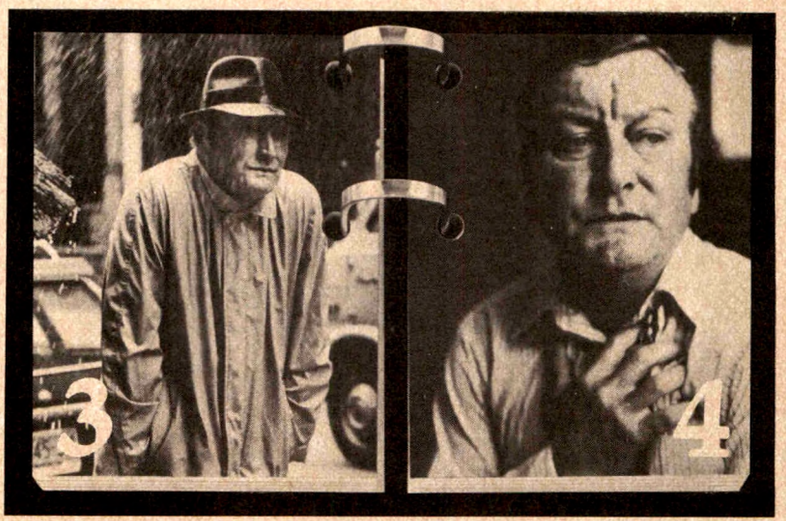

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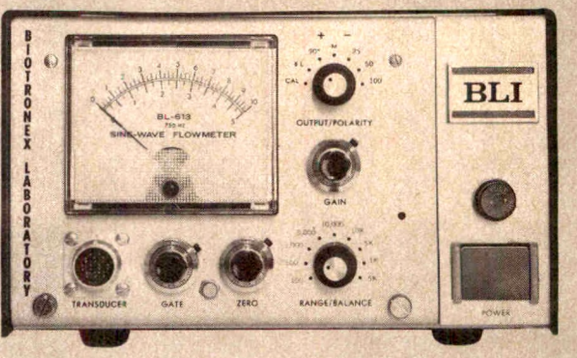

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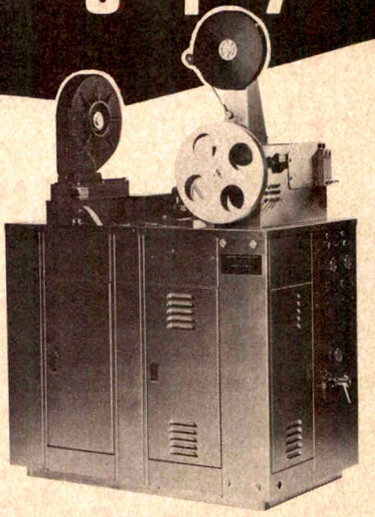

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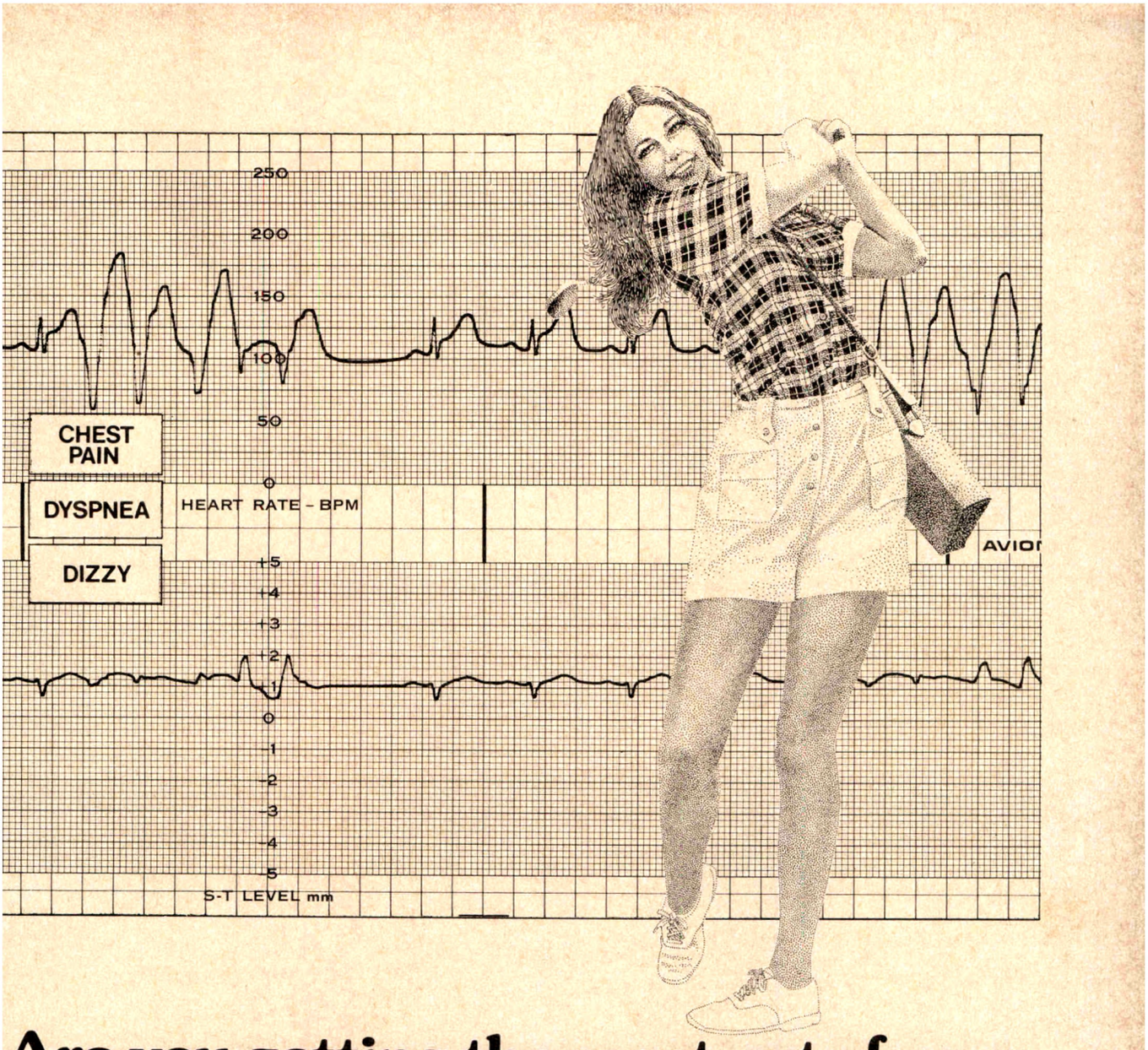

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The ideal solution to monitoring Post-Acute Cardiac Patients

A miniature, battery powered transmitter that measures and broadcasts heart rate and QRS wave form to a central nurses' station is the only instrument physically attached to the patient.

LSE Telemetry Monitors provide accurate and continuous data of ambulatory patient's heart signal during recovery, within a range of 300 feet in open space and to more than 1000 feet with antenna. The portable versions are also invaluable for emergency arrivals, crash carts, in the operating room and for stress test applications.

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Removal from "hard-wiring" improves psychological outlook while regained mobility helps to improve muscle tone and circulation.

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- No special installation or wiring . . . Just plug it in.
- Systems interface with diagnostic computers, data phones, remote recorders and displays.
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LSE offers a broad variety of complete Telemetry Cardiac Monitoring Products including:

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- **Portable Bedside Monitors** — with many of the above features, including battery or AC operation, up to 11 different patient transmitters, displays one patient at a time, used in combination with single or multiple-external recorde

For complete information, send for our new, Free Brochure today!

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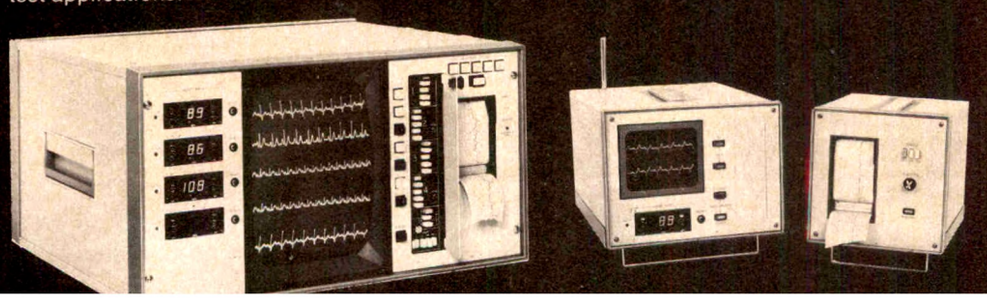

LSE

LASER SYSTEMS & ELECTRONICS, INC.
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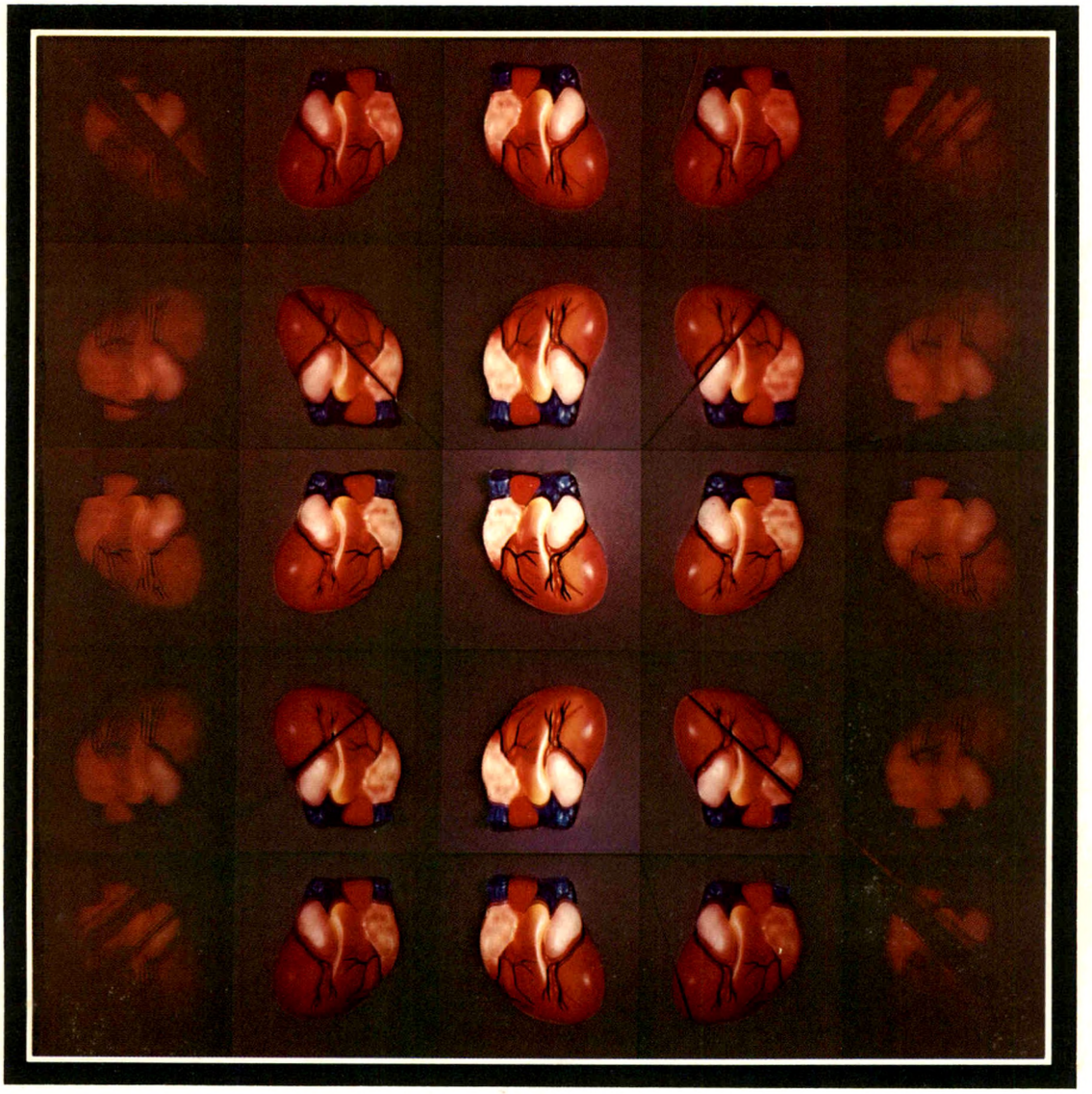
In the shock syndrome due to myocardial infarction



See last page of this advertisement for full prescribing information.

The drug for the heart that reflects itself in the kidney

INTROPIN®
(dopamine HCl)

Intropin® (dopamine HCl) provides a positive approach in the correction of hemodynamic imbalances in the shock syndrome due to myocardial infarction. Intropin is a drug to consider after you have established an adequate airway and corrected existing hypovolemia.

Intropin is a unique catecholamine that does what you want it to do – increase cardiac output, increase vital organ perfusion and increase urine output without increasing the likelihood of serious undesirable effects.

A key to increased survival of the shock episode is to initiate Intropin therapy as soon as practical after the onset of signs, since the patients most likely to respond are those whose myocardial function, urine output and blood pressure have not undergone profound deterioration. The less time between onset of signs and the initiation of shock therapy, the better the prognosis.

Intropin must be diluted in a suitable intravenous solution and given by I. V. drip.

Increase vital organ perfusion and urine output

Intropin provides increased vital organ perfusion and can significantly increase urine flow in the low-to-moderate dosage range. Increased urine output (plus accompanying sodium excretion) is caused by an increase in the renal blood flow and glomerular filtration.

In contrast, other catecholamines do not consistently increase (and often decrease) urine output.

Intropin may also increase urine output in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation.

When high doses (above 30 mcg/kg/min) of Intropin are administered, urine flow may decrease, and a dosage reduction may be necessary.

Increase in cardiac output, stroke volume and contractility

Intropin substantially increases contractility, stroke volume and cardiac output by acting on the beta receptors of the heart.

The myocardial oxygen supply/demand ratio appears to remain stable with Intropin at low to intermediate doses. Intropin produces less increase in myocardial oxygen consumption than isoproterenol.

Increase blood pressure

Low-to-moderate doses of Intropin are usually sufficient to manage hypotension due to inadequate cardiac output. At these doses, Intropin does not typically increase total peripheral vascular resistance. Blood flow to the mesenteric area may increase while circulation in the peripheral vascular beds may decrease.

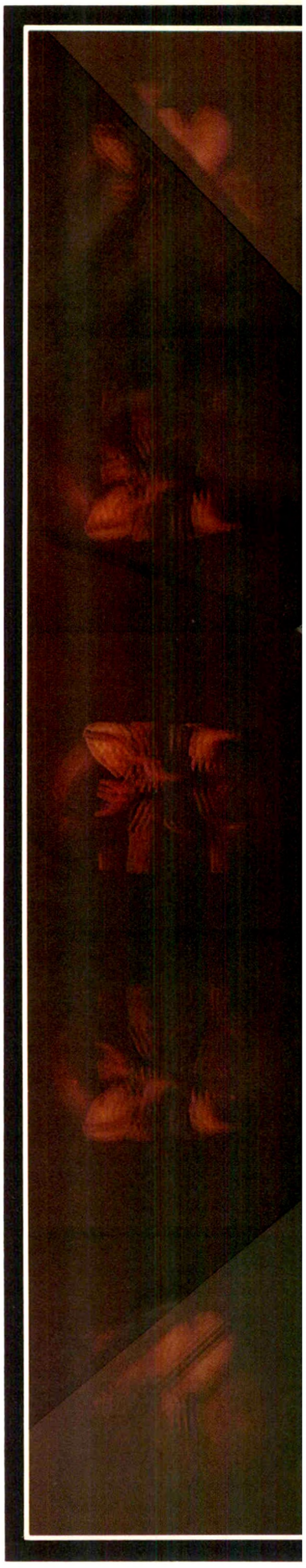
Before administering Intropin, the physician should be familiar with the effects of the drug at various dose levels (see chart). Note especially the paradoxical results of Intropin at the higher ranges (over 30 mcg/kg/min) – increased systemic vascular resistance plus a decrease in renal blood flow and urine output. These phenomena can be reversed, if desired, by reducing the dose.

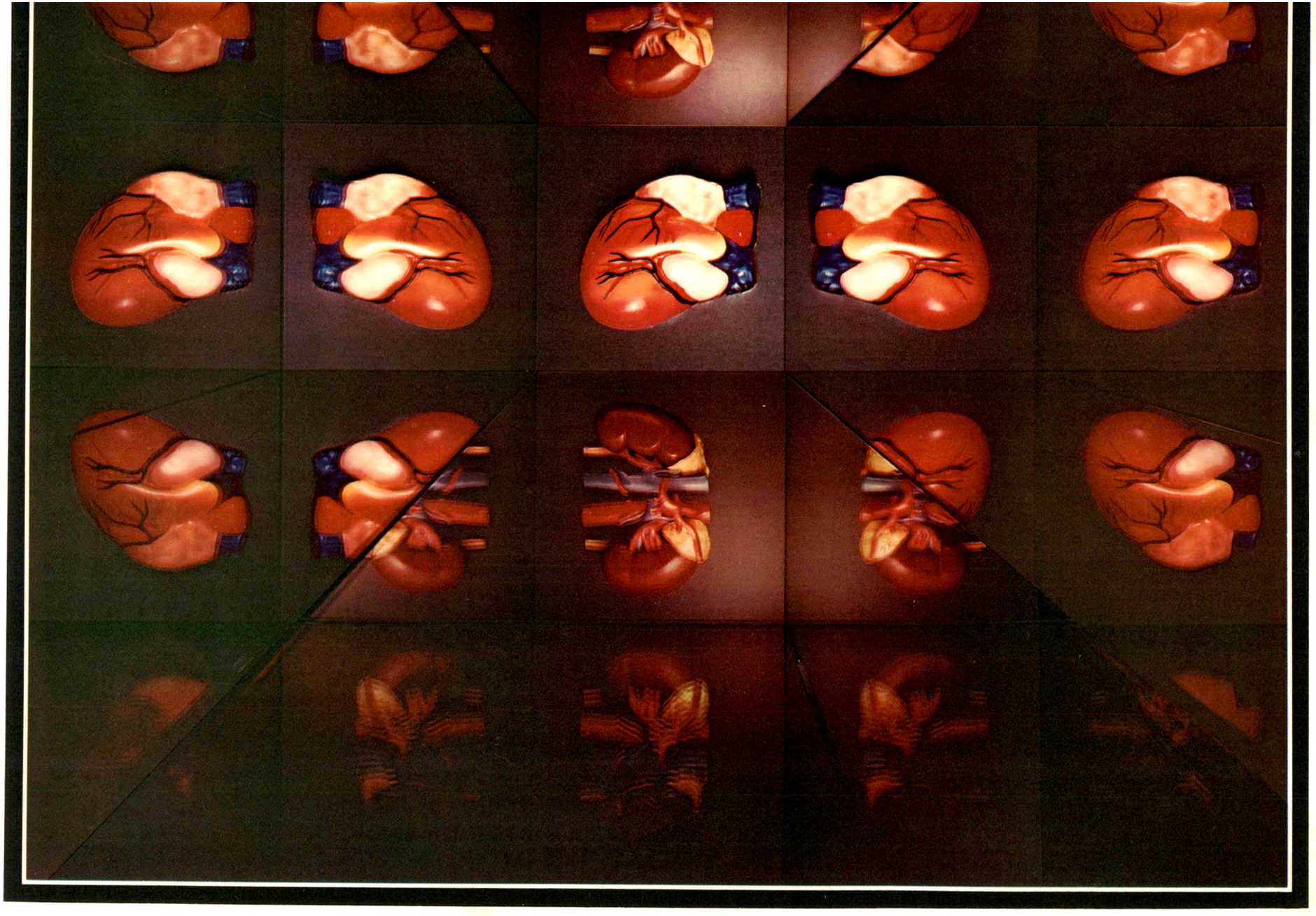
Increase dosage control

Intropin has a half life of approximately 1.75 minutes, and the positive effects of the drug usually dissipate within 10 minutes after discontinuing the medication.

As shown in the chart, the positive effects of Intropin vary with the dose levels administered. Before using the drug, physicians are advised to familiarize themselves with the Intropin dose phenomena – particularly as they relate to the kidney.

See last page of this advertisement for full prescribing information.





The effects of Intropin® (dopamine HCl) at low, intermediate and high dose levels

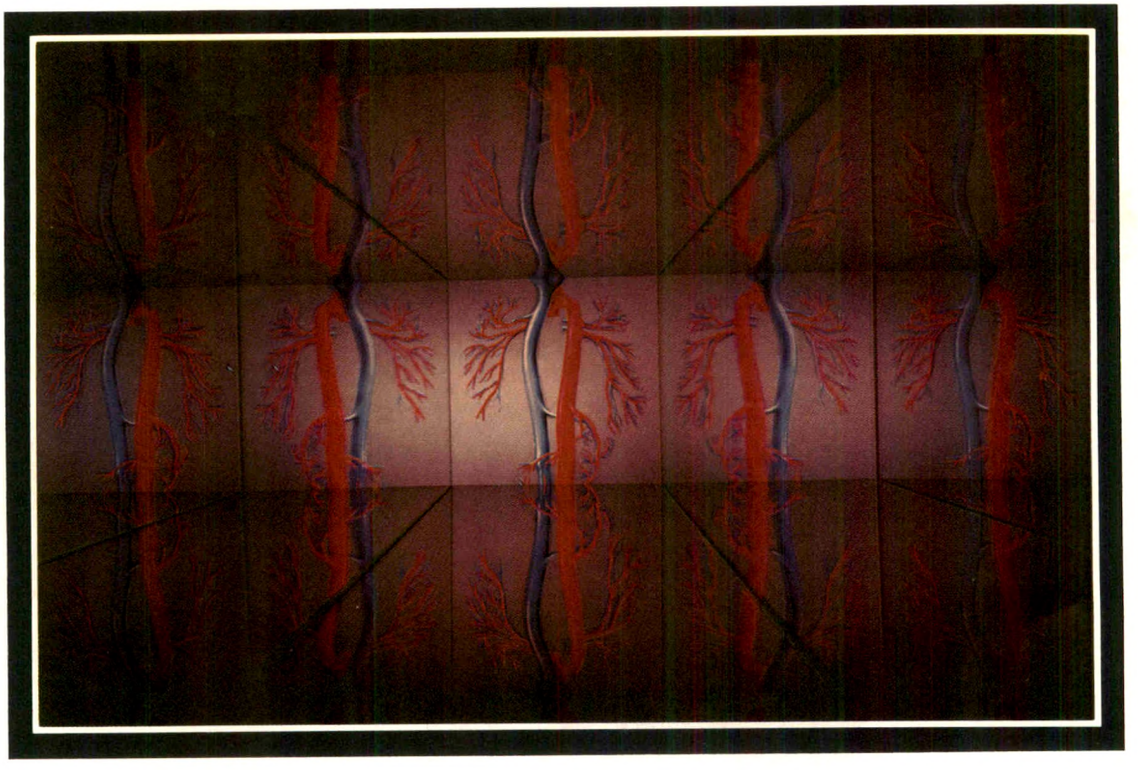
	Low Dose 2-5 mcg/kg/min	Intermediate Dose 5-30 mcg/kg/min	High Dose over 30 mcg/kg/min
Cardiac Output	no change	increase	increase
Stroke Volume	no change	increase	increase
Heart Rate	no change	there is an initial increase followed by a decrease toward normal rate as infusion continues	
Myocardial Contractility	no change	increase	increase
*Potential for Excessive Myocardial Oxygen Demands	low coronary blood flow increased	low coronary blood flow increased	data unavailable
*Potential for Tachyarrhythmias	low	low	moderate
Total Systemic Vascular Resistance	slight decrease to no change	no change to slight increase	increase
Renal Blood Flow	increase	increase	decrease
Urine Output	increase	increase	decrease

Intropin educational materials available

Useful Intropin educational materials (including dosage converters; training kits for critical care personnel; a 20-minute instructional film with accompanying literature; and published clinical reprints) may be obtained through your Arnar-Stone representative, or by contacting Arnar-Stone Laboratories, Inc., directly.

See last page of this advertisement for full prescribing information.

*Low but needs monitoring



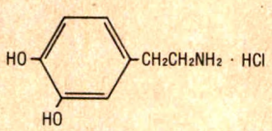
ARNAR-STONE LABORATORIES, INC.
601 E. Kensington Rd.
Mt. Prospect, Illinois 60056

Printed in U.S.A. /ASL-08-75-932

INTROPIN® (dopamine HCl)

5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3,4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs—Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output—Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension—Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy—Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children—The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia—Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure—If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation—INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease—Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT—Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics—Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required—Close monitoring of the following indices—urine flow, cardiac output and blood pressure—during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution—Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration—INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.
2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.
4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter.

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New Saunders Titles (they're worth monitoring)

STEIN: The Electrocardiogram: A Self-Study Course in Clinical Electrocardiography

An excellent audio-visual program which provides a complete foundational course in the proper interpretation and understanding of the clinical electrocardiogram. All important aspects of general electrocardiography are examined. The ten C-60 cassette tapes present polished lectures that are carefully correlated to the illustrations and text in the manual. Grant's spatial vector approach is emphasized in the instruction.

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KRIKLER & GOODWIN: Cardiac Arrhythmias: The Modern Electrophysiological Approach

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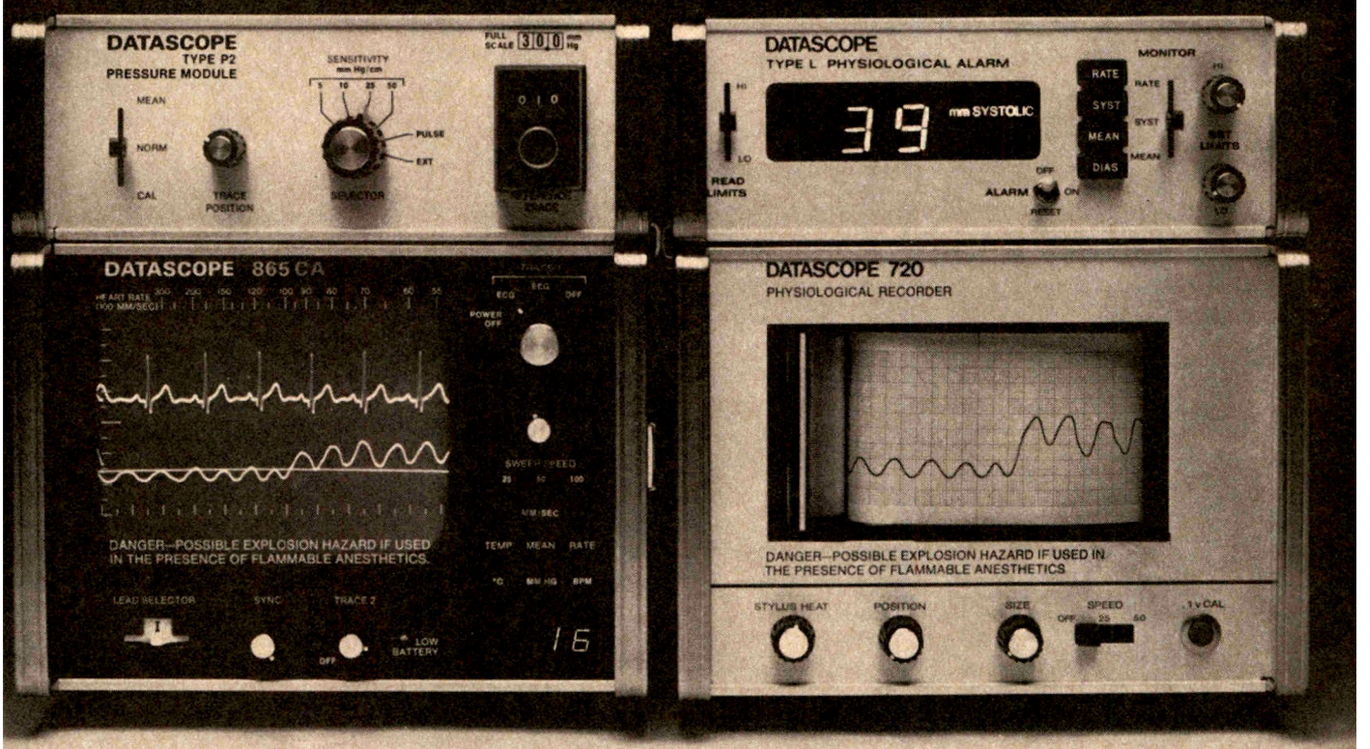

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So you don't have to have a unit for every bed.

Which not only makes life simpler for the people who use it, but also for the people who buy it.

For more information on the Datascope Wedge Pressure Group, write: Datascope Corp., 580 Winters Ave., Paramus, N.J. 07652.

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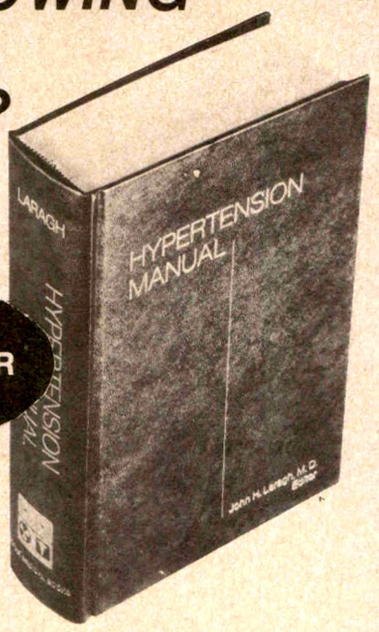

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Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

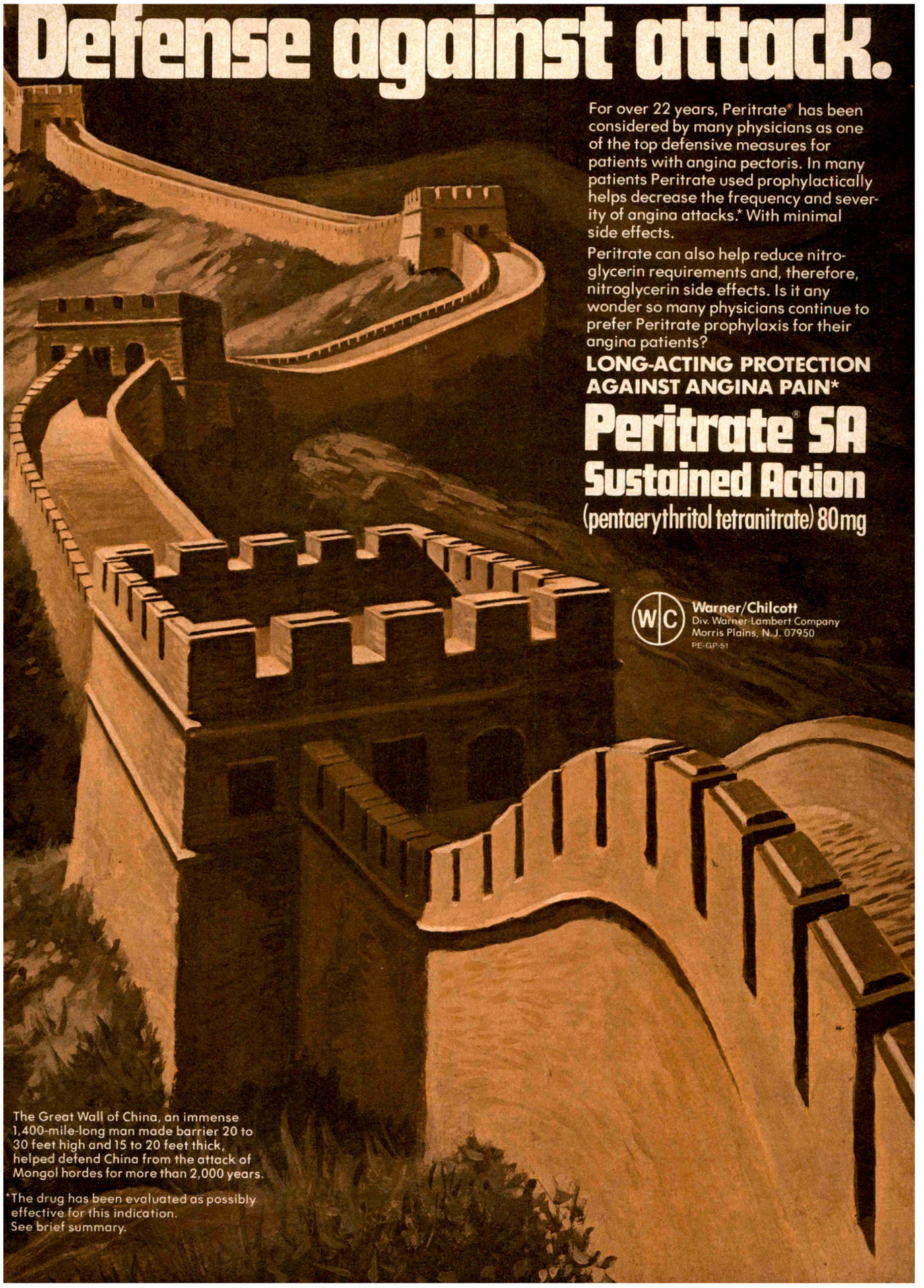
Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later. Tablets should not be chewed.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also in unit dose—package of 10 x 10 strips (N 0047-0004-11).

Additional Dosage Forms: Peritrate 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also in unit dose—package of 10 x 10 strips (N 0047-0001-11). Peritrate 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

Full information is available on request.

Defense against attack.



For over 22 years, Peritrate® has been considered by many physicians as one of the top defensive measures for patients with angina pectoris. In many patients Peritrate used prophylactically helps decrease the frequency and severity of angina attacks.* With minimal side effects.

Peritrate can also help reduce nitroglycerin requirements and, therefore, nitroglycerin side effects. Is it any wonder so many physicians continue to prefer Peritrate prophylaxis for their angina patients?

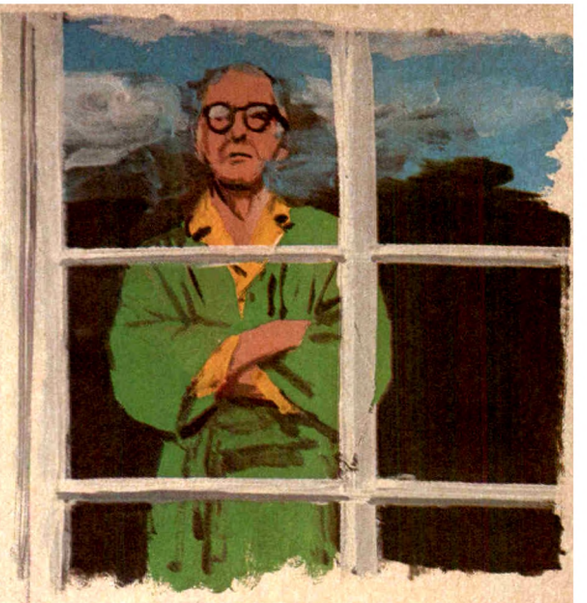
LONG-ACTING PROTECTION AGAINST ANGINA PAIN*

Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) 80mg

Warner/Chilcott
Div. Warner-Lambert Company
Morris Plains, N.J. 07950
PE-GP-51

The Great Wall of China, an immense 1,400-mile-long man made barrier 20 to 30 feet high and 15 to 20 feet thick, helped defend China from the attack of Mongol hordes for more than 2,000 years.

*The drug has been evaluated as possibly effective for this indication.
See brief summary.

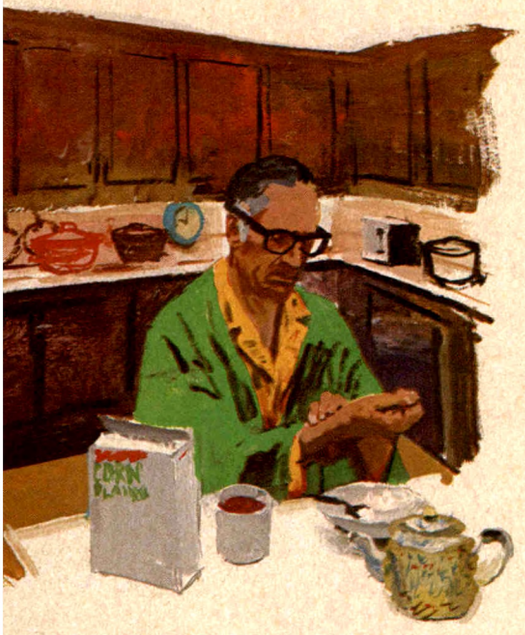


Another day lost.

A cardiac patient's anxiety
and associated depressive symptoms
can often delay active participation
in rehabilitation for days or even weeks.

ROCHE

In the hospital's protective atmos-
ere, the cardiac patient may have
med reasonably calm and coopera-
e—well on his way to the kind of emo-
nal adjustment that many patients
nage to make after a heart attack. But
w he's back home, and must face the
owledge that life may never again be
te the same. Suddenly, he may be-
ne more anxious than he's ever been
ore. More fearful about the future.
d his steadily mounting anxiety and
sion—often accompanied by associ-
d depressive symptoms—can make it
icult for him to attempt rehabilitation.



In time, many such patients respond
l to your continued support and
nseling efforts. But when excessive
chic tension—with or without associ-
l depressive features—continues to
ede rehabilitative progress, Valium
azepam) can be extremely helpful.
e psychotherapeutic effect of Valium
requently both pronounced and
id: quite often, the patient experi-
es significant relief of emotional dis-
s during the first few days of therapy
l is, therefore, ready that much
ner to take a more active part in his
n recovery. (Some patients, of
urse, may require more time to obtain
ear-cut response.)

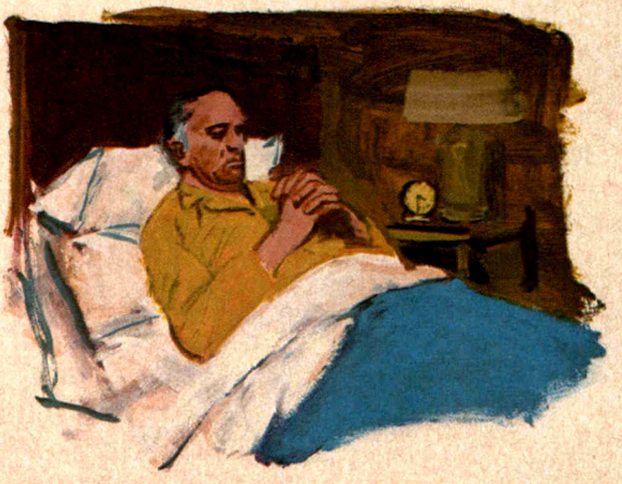
An important advantage in treating the cardiac patient: Valium (diazepam) is used with most classes of primary medications such as cardiac glycosides, anticoagulants, diuretics and vasodilators. Since it's available as scored tablets, Valium allows you to set, adjust and readjust dosage as appropriate during therapy. And it's often helpful to add an *h.s.* dose to a *b.i.d.* or *t.i.d.* regimen if the patient's anxiety and secondary depressive symptoms worsen at bedtime.

In recommended doses, oral Valium generally does not cause significant adverse effects on vital signs; however, lower initial doses (2 to 2½ mg once or twice daily) should be used with elderly or debilitated patients to help avoid ataxia or oversedation. Physicians should be aware of the possibility of other side effects described in complete product information.

Before prescribing, please see complete product information, a summary of which appears on the next page.

Valium®
(diazepam)

2-mg, 5-mg, 10-mg scored tablets



For the cardiac patient's psychoneurotic anxiety and associated depressive symptoms.

Valium® (diazepam)

2-mg, 5-mg, 10-mg scored tablets

Prompt and effective action
Valium acts promptly to help relieve psychic tension and its associated depressive symptoms in the psychoneurotic cardiac patient.

Wide margin of safety
At recommended dosages, oral Valium is generally well tolerated and does not significantly affect respiration, pulse or heart rate.

Flexible dosage
Valium, available as 2-mg, 5-mg and 10-mg *scor* tablets, allows dosage to be easily readjusted to suit patients' changing needs.

Predictable pharmacokinetically
Pharmacokinetic studies of Valium demonstrate highly predictable pattern of absorption, distrib tion, metabolism and excretion.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautio indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Lim dosage to smallest effective amount in elderly and deb itated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depres sion, dysarthria, jaundice, skin rash, ataxia, constipatic headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcite states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; perio blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 1 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patient* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 t 2½ mg t.i.d. or q.i.d. initially, increasing as needed an tolerated (not for use under 6 months).

Supplied: Valium®(diazepam) Tablets, 2 mg, 5 and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numb boxes of 25, and in boxes containing 10 strips of 10; I scription Paks of 50, available singly and in trays of 1

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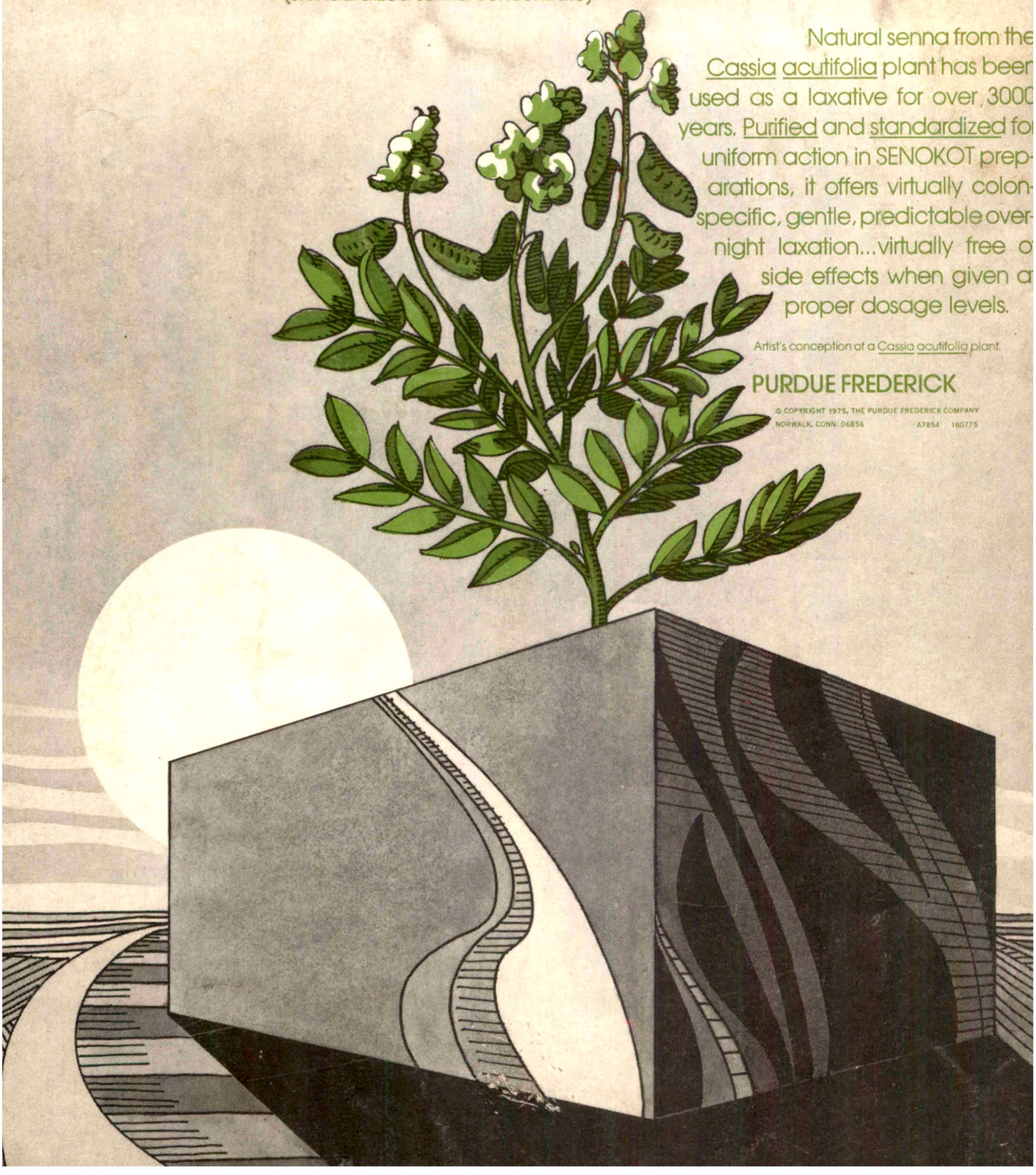
In this age of synthetics you can choose a natural vegetable laxative

Senokot® tablets granules

(standardized senna concentrate)



Natural senna from the Cassia acutifolia plant has been used as a laxative for over 3000 years. Purified and standardized for uniform action in SENOKOT preparations, it offers virtually colon-specific, gentle, predictable overnight laxation...virtually free of side effects when given at proper dosage levels.

Artist's conception of a Cassia acutifolia plant.

PURDUE FREDERICK

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DECEMBER 1975

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OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Electrophysiologic Studies in Transplanted Hearts

Myocardial Glucose and Lipid Metabolism During Infarction

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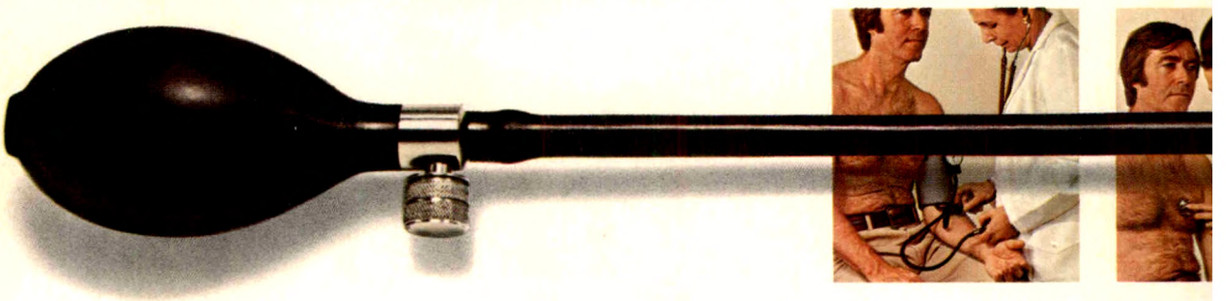
WHEN DRUG TREATMENT BEGINS...



addendum

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AND THROUGHOUT THE YEARS

OF ANTIHYPERTENSIVE THERAPY

When drug therapy is indicated in hypertension, HydroDIURIL has proven to be a clinically useful baseline agent

The antihypertensive effect of HydroDIURIL is usually maintained throughout long-term therapy

When additional therapy is warranted, HydroDIURIL may be used in combination with other antihypertensive agents. HydroDIURIL may add to or potentiate the action of other antihypertensive drugs. Therefore, careful observations for changes in blood pressure must be made.

Contraindications include anuria and hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs. Use with caution in patients with severe renal disease, impaired hepatic function, or progressive liver disease.

TABLETS, 25 mg, 50 mg, and 100 mg

HydroDIURIL®
(Hydrochlorothiazide | MSD)

highly effective, single-entity antihypertensive

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

"Required Reading" For Your Hypertensive Patients

Because of the importance of patient motivation, Merck Sharp & Dohme offers "High Blood Pressure," a concise, pocket-sized booklet that defines the patient's own role in the management of hypertension. This booklet is available for you to give to your patients. It is designed to reinforce your explanation of hypertension and it emphasizes the importance of patient understanding in adhering to the regimen you prescribe.

Please ask your Merck Sharp & Dohme Professional Representative or write Professional Service Department, West Point, Pa. 19486 for a supply of this booklet.

THROUGHOUT THE YEARS OF ANTIHYPERTENSIVE THERAPY

HydroDIURIL®
(Hydrochlorothiazide | MSD)

highly effective, single-entity antihypertensive

Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs; routine use in an otherwise healthy pregnant woman with or without mild edema.

Warnings: Use with caution in severe renal disease since thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

Use in pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy or in women of childbearing potential, weigh anticipated benefit against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.

Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

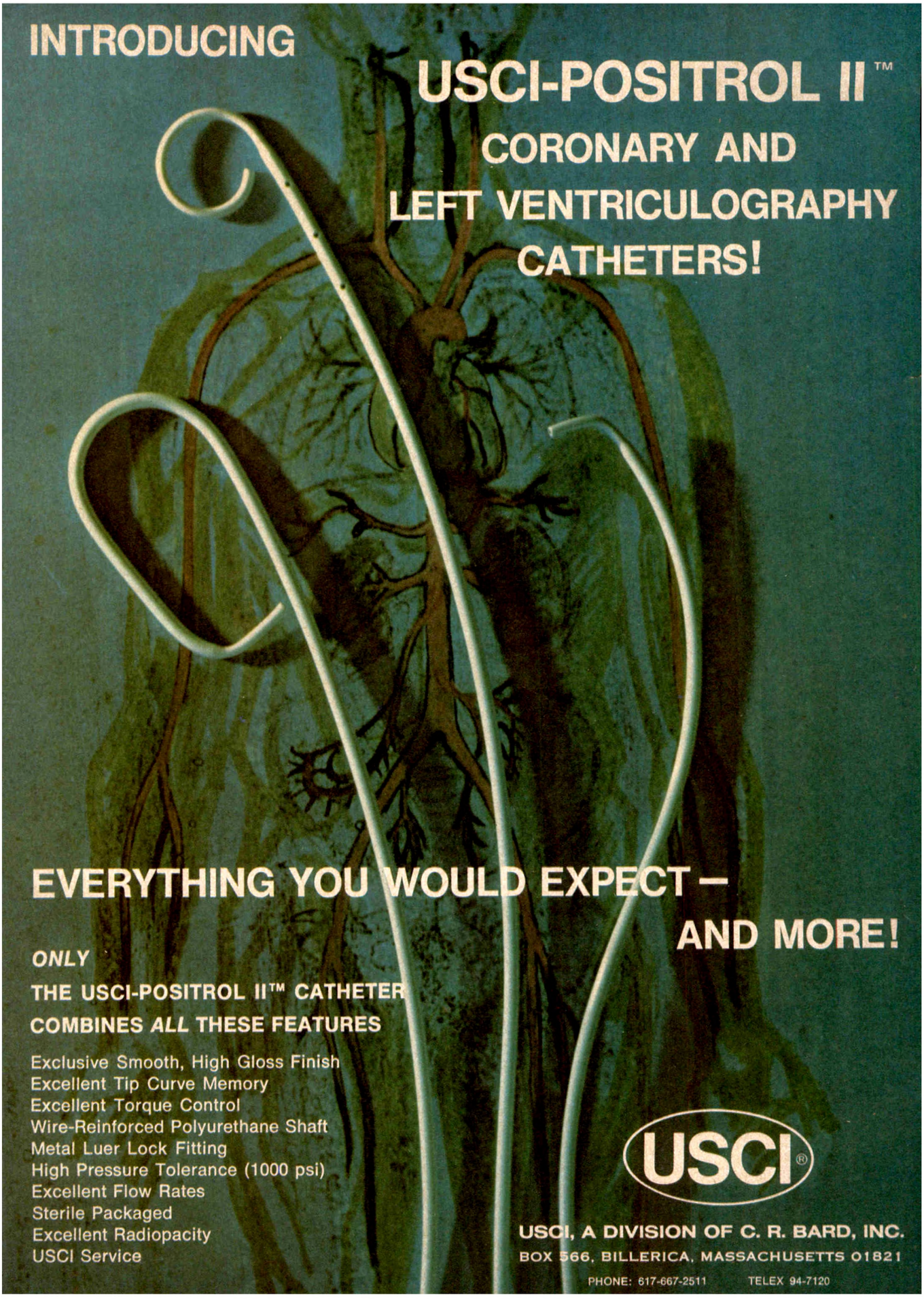
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 25 mg hydrochlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 50 mg hydrochlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Tablets containing 100 mg hydrochlorothiazide each in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

MSD
MERCK SHARP & DOHME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Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F) and 25 mg. of hydrochlorothiazide.

MAKES SENSE

TRIAMTERENE CONSERVES POTASSIUM WHILE HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE

FOR LONG-TERM CONTROL OF HYPERTENSION*

Serum K^+ and BUN should be checked periodically. (See Warnings Section.)

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Warning**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

***Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

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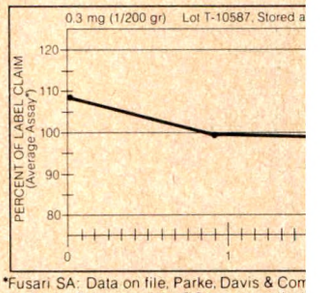

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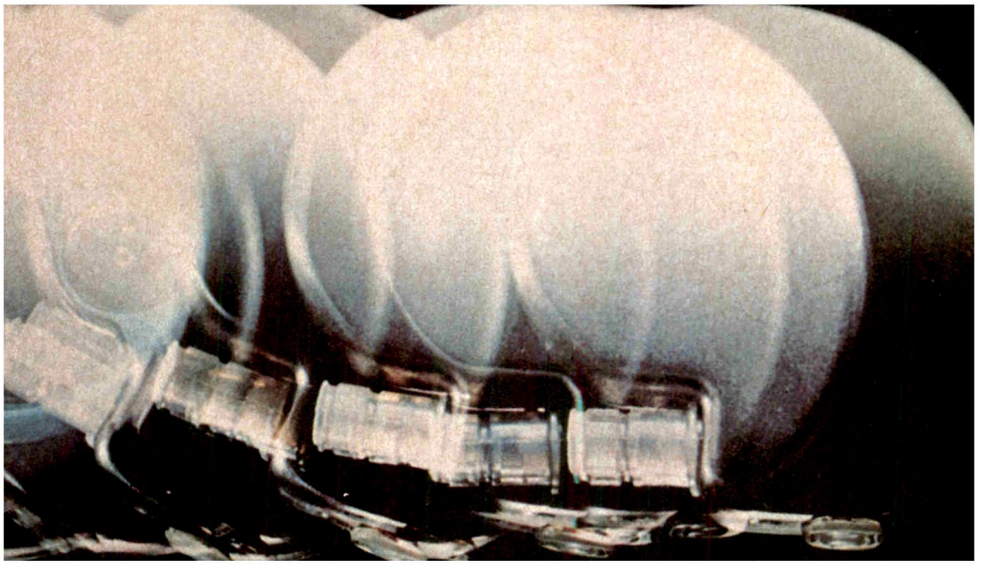

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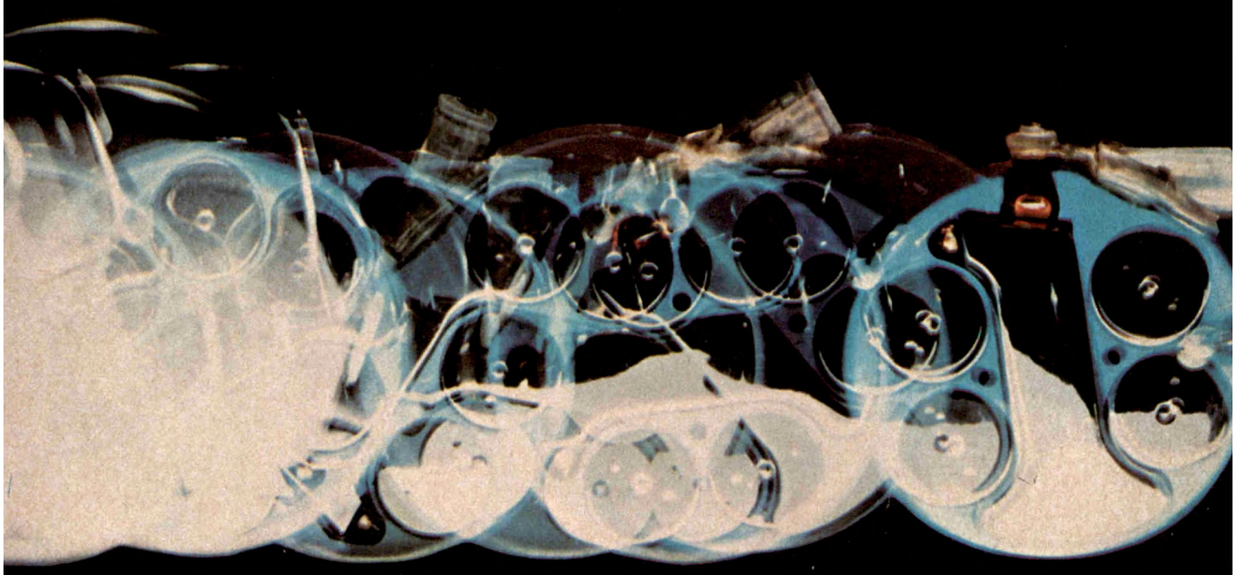

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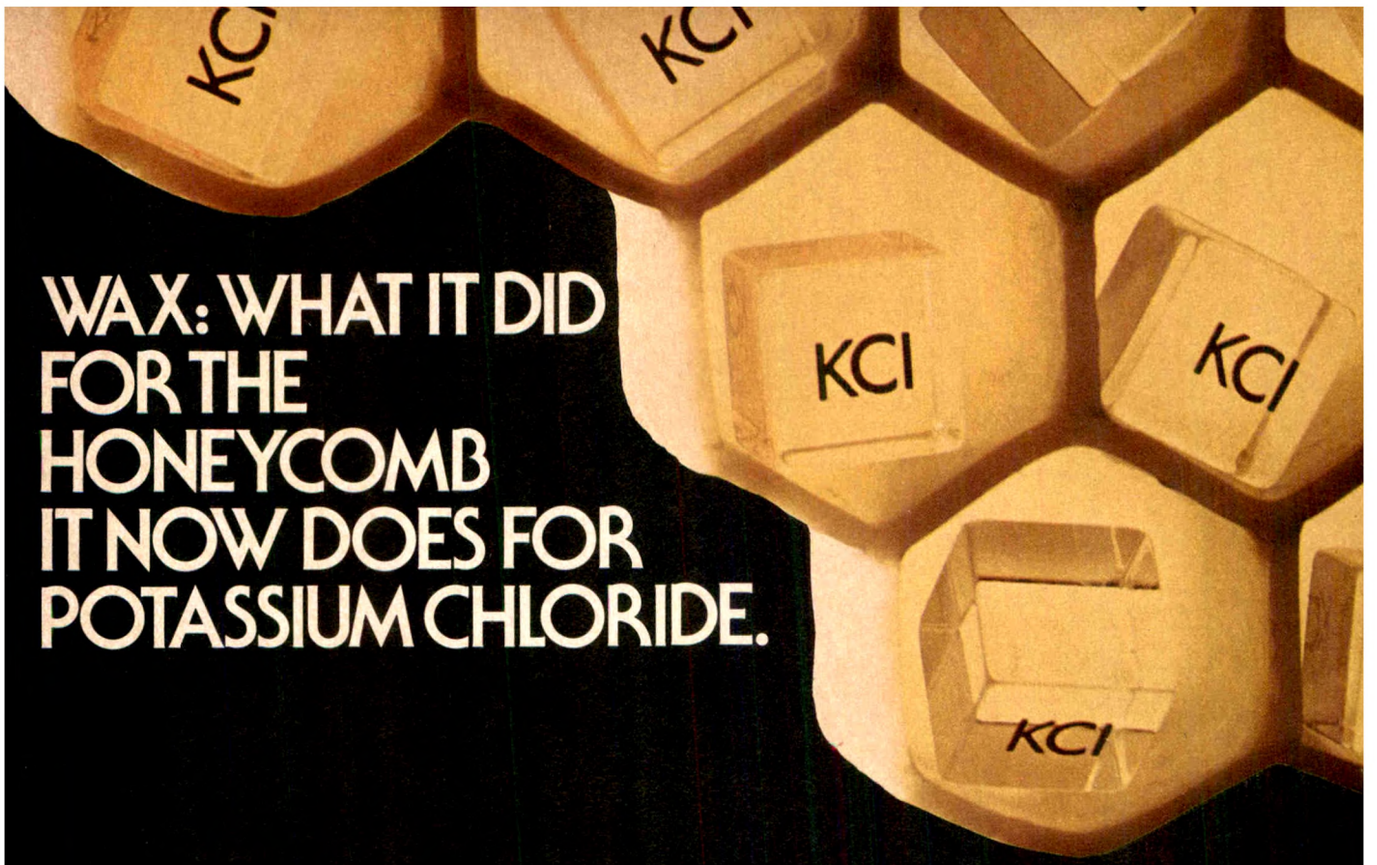


WAX: WHAT IT DID FOR THE HONEYCOMB IT NOW DOES FOR POTASSIUM CHLORIDE.

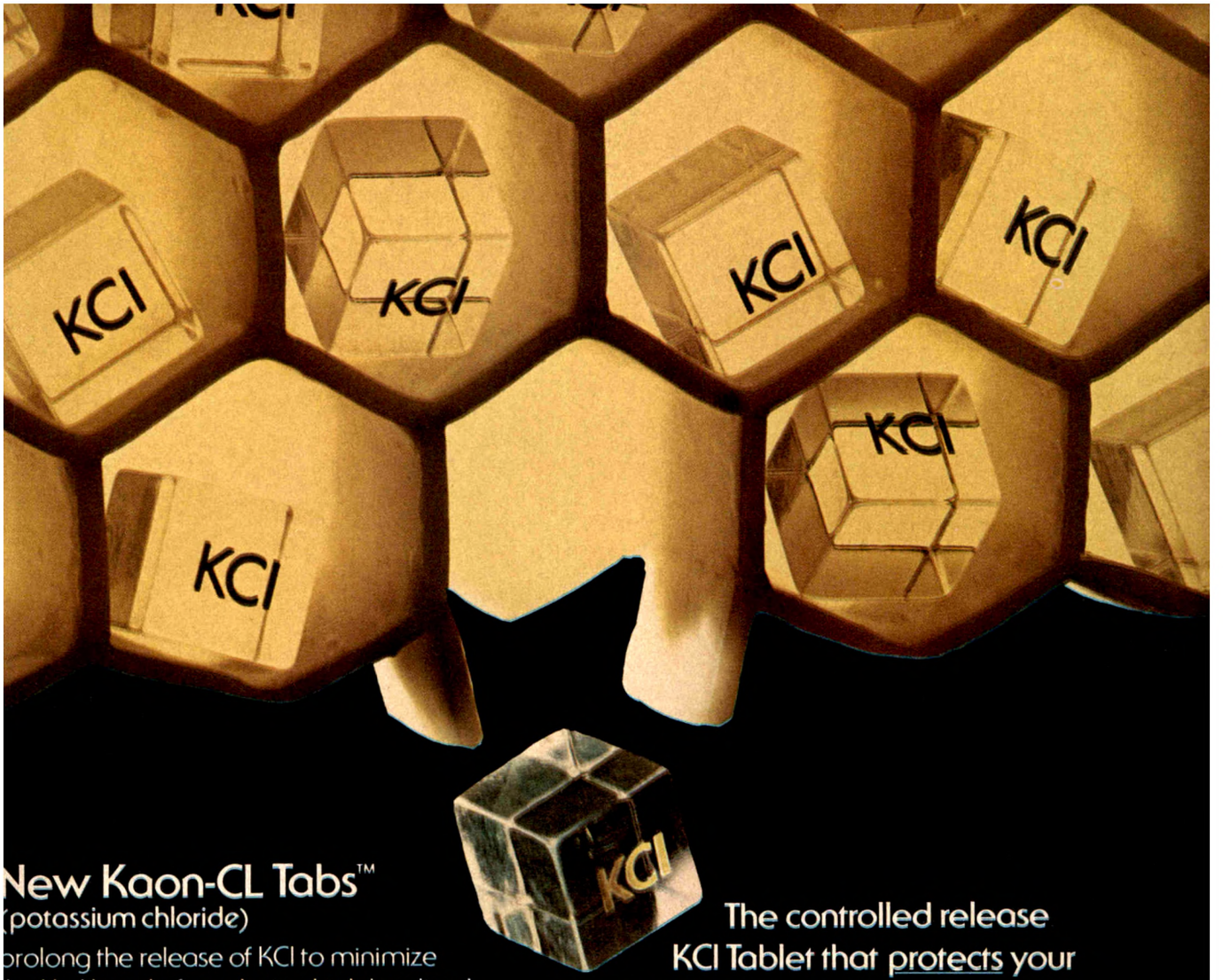
WARREN-TEED® ANNOUNCES

NEW KAON-CL TABS™

(potassium chloride)

CONTROLLED RELEASE TABLETS

– Potassium chloride imbedded in a wax matrix to provide controlled release, thus minimizing possible high local concentration of potassium ion near the bowel wall. The newest idea in potassium chloride supplements is as old as the beehive. Wax... provides an effective vehicle to imbed KCl crystals for a controlled rate of release



New Kaon-CL Tabs™
(potassium chloride)

prolong the release of KCl to minimize the likelihood of producing high localized concentrations of potassium within the G.I. tract...

protect your patient from the risk of hypokalemia or digitalis intoxication due to potassium depletion that diet alone cannot correct...

promote adherence to medication schedule by relieving the patient of the inconvenience of liquids...

Three-way convenience for your patients on KCl Supplements...

because there's no palatability problem

because there's no dilution problem

because tablets are physically easier to carry—and to take—than liquids...
an especially welcome advantage away from home—encouraging adherence

The controlled release KCl Tablet that protects your patients on diuretics or digitalis

- against hypokalemia due to potassium depletion that cannot be adequately replaced by diet alone
- against the inconvenience of—and often confusion over—dilution of liquid supplements
- from taste-fatigue associated with liquids

Dosage: Prophylactic: 20 mEq. daily (1 tab T.I.D.)
Therapeutic: 40-100 mEq. daily
See following page for brief summary.

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KAON-CL TABS™

(Potassium Chloride)

CONTROLLED RELEASE TABLETS

Description: Kaon-CL Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg. potassium chloride (equivalent to 6.67 mEq. potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: Kaon-CL Tabs is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. Kaon-CL Tabs is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

Warnings: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-CL Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric coated potassium chloride tablets (40-50 per 100,000 patient-years), a few cases associated with wax-matrix tablets have been reported. These data are from foreign marketing experience. Kaon-CL Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia, in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Dosage and Administration: Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq. per day for the prevention of hypokalemia to 40-100 mEq. per day or more for the treatment of potassium depletion.

One Kaon-CL Tabs three times daily provides 20 mEq. of potassium chloride. Two Kaon-CL Tabs three times daily provides 40 mEq. of potassium chloride.

Caution: Federal law prohibits dispensing without prescription.

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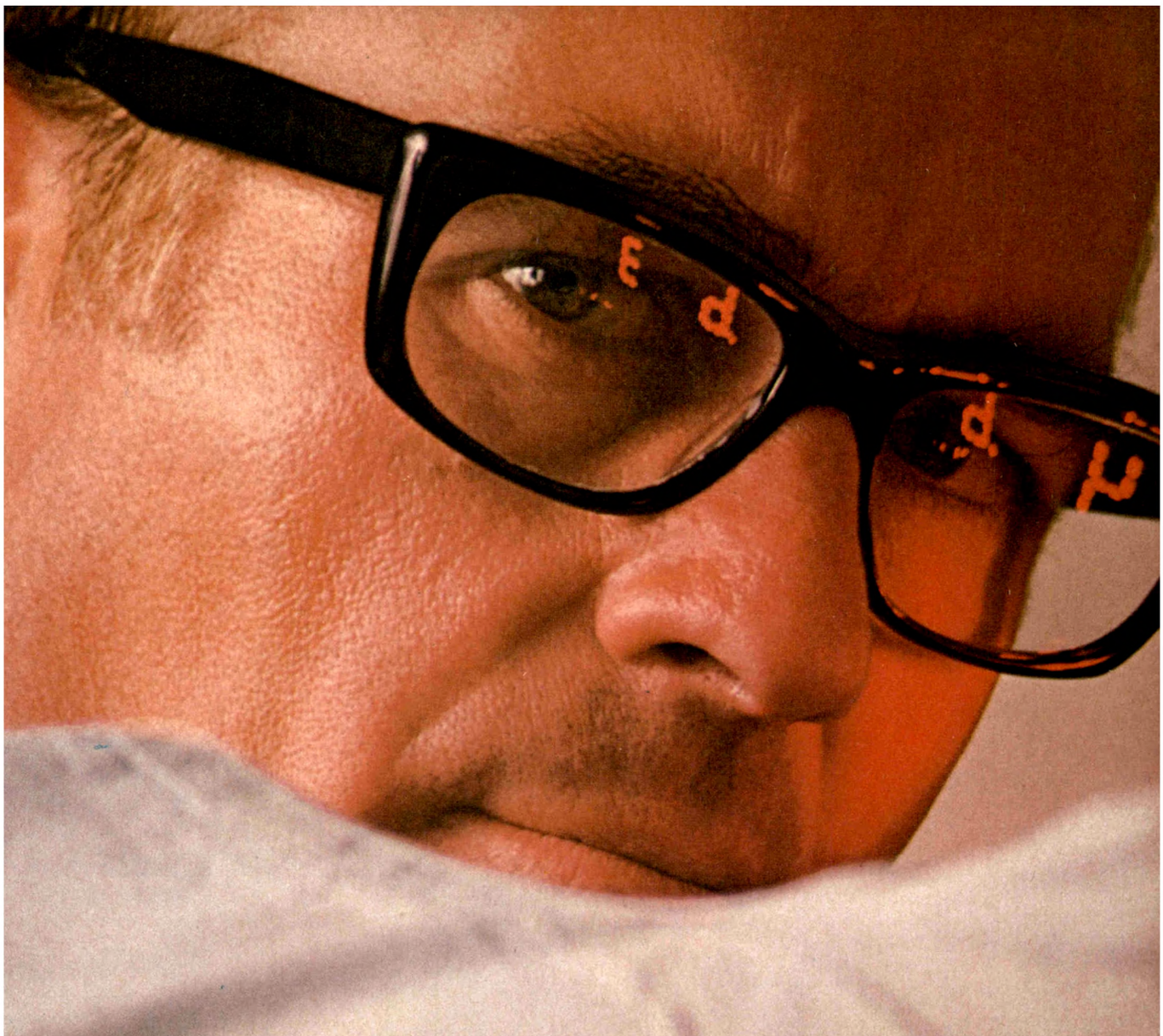

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Both patient temperature **and** injectate temperature are dynamic variables. The ability to rapidly update and fine tune these of various volumes of cold or room temperature injectate, facilitates precise and accurate clinical analysis.

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literature describing the thermodilution cardiac output technique, or a product demonstration, please write Edwards Laboratories, 17221 Red Hill Avenue, P.O. Box 11150, Santa Ana, California 92711, 714/557-8910, Cable: EDSLAB, Telex: 68:5567.

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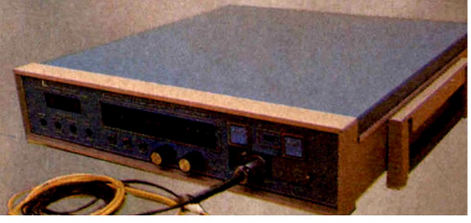

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SIDE EFFECTS: No serious side effects have been reported. In sublingual therapy a tingling sensation (like that of nitroglycerin) may sometimes be noted at the point of tablet contact with the mucous membrane. If objectionable, this may be mitigated by placing the tablet in the buccal pouch. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics.

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1. Russek HI: AM J M Sc 239:478, 1960

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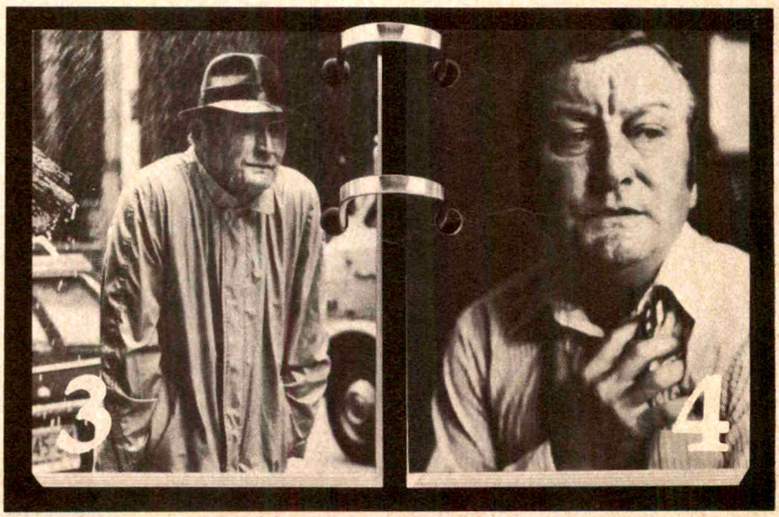

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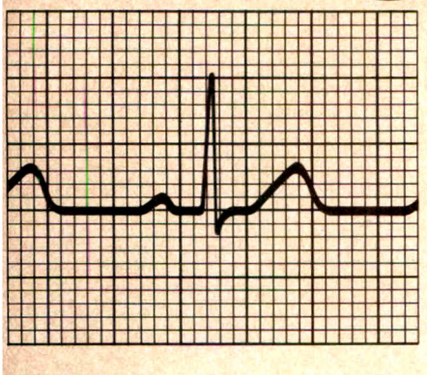
25th Annual Meeting
New Orleans, February 23-26, 1976

How Burdick separates fact from artifact



A stereo with the high-frequency range to tweet the piccolos and the low-frequency response to boom the cannons of "The 1812 Overture" will also hiss the dust of the record. Similarly, an electrocardiograph, such as the Burdick EK-5A, that's hi-fi enough to register minute voltages important to accurate diagnosis, will also register subtle interference, or artifact.

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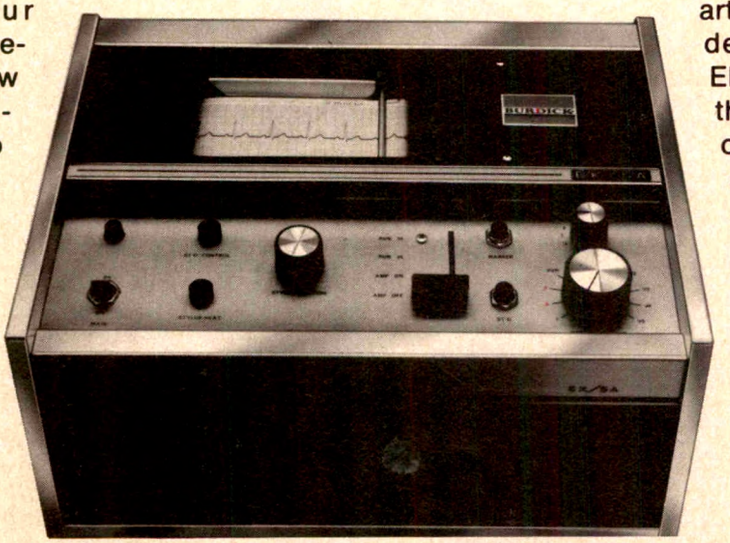

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DAVID S. CANNOM, ALAN K. RIDER, EDWARD B. STINSON and DONALD C. HARRISON

The denervated transplanted human heart, studied in 5 patients by the His bundle technique, appears to respond normally to norepinephrine and isoproterenol. Propranolol blocks their electrophysiologic effects but does not alter the systolic hypertension produced by norepinephrine infusion. These studies in man validate that functional integrity of the beta receptor is maintained even when autonomic nerves are absent and that the intrinsic properties of the S-A and A-V nodes are crucial in stabilizing cardiac electrophysiology after denervation.

867 Chronic Right Bundle Branch Block and Left Posterior Hemiblock. Clinical, Electrophysiologic and Prognostic Observations

RAMESH C. DHINGRA, PABLO DENES, DELON WU, RUBEN CHUQUIMIA, FERNANDO AMAT-Y-LEON, CHRISTOPHER WYNDHAM and KENNETH M. ROSEN

Only 3 of 21 patients (14 percent) with chronic right bundle branch block and left posterior hemiblock, followed up prospectively for 29 to 1,231 days, required a permanent pacemaker after manifesting symptomatic S-A block, second degree A-V block (site undetermined) or A-V block proximal to the His bundle. These data suggest that patients with this conduction defect do not require routine prophylactic pacemaker insertion since it is associated with less trifascicular disease than previously reported, its clinical course is benign and the incidence of sudden death in such patients is relatively small.

873 First Derivative of the Apex Cardiogram and Systolic Time Intervals in Evaluation of Myocardial Contractility in Man

JOS L. WILLEMS, MARY C. KYLE, HAROLD C. PILLSBURY, III and EDWARD D. FREIS

Comparison of the sensitivity of different systolic time intervals and measurements derived from dp/dt of the apex cardiogram in 15 normal subjects before and after the administration of angiotensin, isoproterenol and propranolol revealed significant changes, mainly in the early phases of the cardiac contraction cycle. These results suggest that the ratio (dp/dt)/P derived from the calibrated apex cardiogram is comparable to the same ratio derived from left ventricular pressure and may be a useful new noninvasive index of myocardial contractility.

880 Mahaim and James Fibers As a Basis for a Unique Variety of Ventricular Preexcitation

MAURICE LEV, SAMUEL M. FOX, III, SAROJA BHARATI, JOSEPH C. GREENFIELD, Jr., KENNETH M. ROSEN and ALFRED PICK

This unique case of intermittent ventricular preexcitation syndrome defies classification into any known variety. Serial sections of the conducting system of the heart revealed no bundle of Kent but demonstrated that Mahaim fibers histologically identified as His bundle tissue gave off from the A-V bundle to both sides of the septum associated with the normal James fibers. Mahaim fibers, therefore, can conduct and James fibers can bypass the A-V node.

Continued on page A19

Beat after beat...day after day

CARDIOQUIN tablets

(quinidine polygalacturonate)

To convert...to MAINTAIN normal sinus rhythm

After conversion of cardiac arrhythmias—whether with CARDIOQUIN Tablets or some other current method—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required in most cases to maintain normal sinus rhythm.

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*Aviado, D. M., *Krantz and Carr's Pharmacologic Principles of Medical Practice*, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heartblock; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and main- used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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889 Disappearance of Abnormal Q Waves After Aortocoronary Bypass Surgery

CESAR A. CONDE, JOSE MELLER, JAIME ESPINOZA, EPHRAIM DONOSO and SIMON DACK

Following aortocoronary artery bypass surgery 3 of 36 patients lost their preoperative abnormal Q waves, presumably as a result of improved perfusion and electrical activity of the myocardial cells in the area surrounding the infarct.

EXPERIMENTAL STUDIES

894 Comparative Cardiac Dynamic Effects of Dobutamine and Isoproterenol in Conscious Instrumented Dogs

JOSEPH E. HINDS and EDWARD W. HAWTHORNE

Larger doses of dobutamine and isoproterenol both increased all measured indexes of myocardial contractility and cardiac work in conscious healthy instrumented dogs. However, isoproterenol elevated the heart rate more than dobutamine at any given level of contractility. Dobutamine increased the cardiac minute work by improving myocardial contractility without increasing heart rate. These data suggest dobutamine may be a more effective drug for managing myocardial dysfunction than isoproterenol.

902 Effects of Ischemia and Coronary Reperfusion on Myocardial Digoxin Uptake

GEORGE A. BELLER, THOMAS W. SMITH and WILLIAM B. HOOD

Coronary reperfusion after 2 to 6 hours of left coronary occlusion in 17 open chest dogs was associated with a marked reduction in myocardial uptake of tritiated digoxin in the ischemic zone of the left ventricular wall. This was more pronounced in the subendocardial (85 percent) than in the subepicardial (60 percent) regions of the ischemic zone.

PEDIATRIC CARDIOLOGY

908 Echocardiographic Diagnosis of Tetralogy of Fallot

DOUGLAS C. MORRIS, JOEL M. FELNER, ROBERT C. SCHLANT and ROBERT H. FRANCH

Echocardiocardiographic features of tetralogy of Fallot in 25 patients include: (1) an increased right ventricular diameter, (2) thickening of the interventricular septum, (3) narrowing of the right ventricular outflow tract, (4) increased aortic root diameter and (5) overriding of the aorta. The most specific echocardiographic pattern of tetralogy of Fallot is the finding of several echocardiographic abnormalities rather than the single feature of aortic overriding.

914 Congenital and Surgical Atrioventricular Block Within the His Bundle

ANTOINE T. NASRALLAH, PAUL C. GILLETTE and CHARLES E. MULLINS

His bundle recordings localized the site of atrioventricular (A-V) block within the His bundle in three patients with congenital heart disease. Two of these patients had complete A-V heart block and required pacemaker insertion. Complete heart block was congenital in one and surgically induced in the other. More such studies are required to clarify the prognosis of intra-His bundle block.

Continued on page A21

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in minutes, at bedside, without central computer or telephone tie-ins

The Roche Mobile Computerized ECG Station contains its own minicomputer, recorder, and printer. It can eliminate the routine work associated with the reading of normal ECG's. It is highly accurate, classifying correctly 95-98% of normal ECG's, 85% of abnormals.[1] It is fast, supplying a computer printout based on the widely accepted USPHS program within a minute after readings are taken.

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1. Hochberg, H. M., et al.: Automatic electrocardiogram analysis in rapid mass screening. *Arch. Environ. Health* 15:390-398, 1967.

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921 Long-Term Follow-Up of Two Infants with an Implanted Cardiac Pacemaker

SYLVIA P. GRIFFITHS, CONSTANCE J. HAYES, FREDERICK O. BOWMAN, Jr. and WELTON M. GERSONY

Two patients, aged 10 and 8 1/2 years, with congenital heart block who had pacemaker implantation at age 7 and 8 months, respectively, illustrate that pacemaker therapy instituted in infancy can be maintained in childhood without disturbing normal physical and emotional growth.

METHODS

925 Handy Heart Sound Simulator

J. NATHANIEL SANDERSON

This technique utilizing only hands and stethoscope simulates heart auscultatory events readily, accurately and economically and can be used at the bedside to meet the needs of teacher and student.

REPORTS ON THERAPY

929 Effects of Glucose-Insulin-Potassium on Myocardial Substrate Availability and Utilization in Stable Coronary Artery Disease. Studies on Myocardial Carbohydrate, Lipid and Oxygen Arterial-Coronary Sinus Differences in Patients with Coronary Artery Disease

ALFRED W. STANLEY, Jr., ROGER E. MORASKI, RICHARD O. RUSSELL, Jr., WILLIAM J. ROGERS, JOHN A. MANTLE, ROBERT A. KREISBERG, HUEY G. McDANIEL and CHARLES E. RACKLEY

Glucose-insulin-potassium infusion in 14 patients with coronary artery disease increased the arterial glucose and lactate levels and decreased the arterial free fatty acid levels. These and other observations suggest that in such patients glucose-insulin-potassium infusion may significantly diminish myocardial oxygen requirements by reducing myocardial free fatty acid utilization and simultaneous enhancement of myocardial carbohydrate utilization.

REVIEWS

938 Metabolism of Free Fatty Acids, Glucose and Catecholamines in Acute Myocardial Infarction. Relation to Myocardial Ischemia and Infarct Size

LIONEL H. OPIE

Major modifications in the metabolism of free fatty acids, glucose and catecholamines after acute myocardial infarction in man and animals suggest such changes may play a role in modifying infarct size and the development of arrhythmias. Low free fatty acid concentrations are more beneficial to patients with acute myocardial infarction. Recent work demonstrates the beneficial effects of glucose-insulin-potassium in reducing infarct size in the dog, increasing high energy phosphate compounds in the baboon and decreased release of enzyme in the isolated rat heart.

HISTORICAL MILESTONES

954 Carrel and Tuffier (1914) on Experimental Surgery of the Cardiac Orifices

SAUL JARCHO

Although maturing plans for the surgical treatment of valvular disease in man were laid in 1914, 3 decades of additional development were needed before they became truly practical on a broad scale.

Continued on page A23

ACCEPTED CONCEPTS IN ANGINA THERAPY*

- Nitrates are the first line of defense against angina pectoris
- The therapeutic goal of oral nitrate therapy is an angina-free patient

When higher dosage is necessary in the prophylaxis of angina

prescribe

ISORDIL®
(isosorbide dinitrate)
20 mg.

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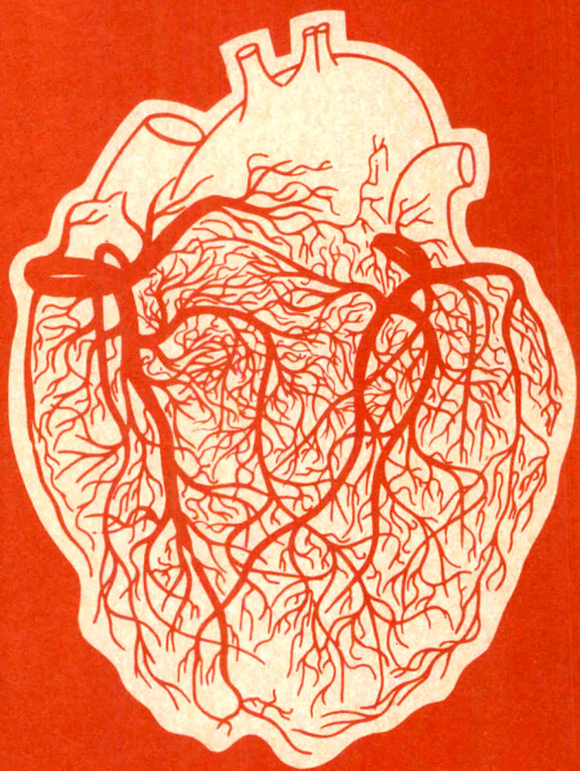

Fewer tablets for patients on 80 mg. or more per day (up to a maximum of 120 mg./day)

- **To provide prophylaxis against anginal attacks often caused by unavoidable everyday stress.**
- **To reduce the frequency and severity of angina pectoris attacks. (Not intended to abort the acute episode.)**

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.
Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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DIAGNOSTIC SHELF

957 Echocardiographic Diagnosis of a Mobile, Pedunculated Tumor in the Left Ventricular Cavity

JORGE A. LEVISMAN, REX N. MacALPIN, ABDUL S. ABBASI, NANCY ELLIS and LESLIE M. EBER

Echocardiography identified a pedunculated thrombus of the left ventricle as the cause of peripheral embolization in a 45 year old woman. At operation the tumor was found to be attached to the interventricular septum by a thin fibrous stalk.

CASE REPORTS

960 Constrictive Pericarditis in Procainamide-Induced Lupus Erythematosus Syndrome

SHUN K. SUNDER and ANILKUMAR SHAH

After consuming only 250 mg of procainamide hydrochloride three times daily for 6 months, procainamide-induced lupus erythematosus with acute pericarditis and pericardial effusion developed in this 47 year old man, possibly as a result of the too rapid withdrawal of steroid therapy leading to deposition of collagen and fibrous tissue in the pericardium. Severe constrictive pericarditis requiring surgery further complicated this patient's clinical course within 6 weeks after the initial symptoms and signs appeared.

963 Severe Alcoholic Cardiomyopathy Reversed with Abstention from Alcohol

LEONARD SCHWARTZ, KAREN A. SAMPLE and E. DOUGLAS WIGLE

This is the first reported case of alcoholic cardiomyopathy in which complete reversibility after 1 year's abstention from alcohol has been documented by cardiac catheterization and angiographic studies. Such recovery occurred without restriction of the patient's activity.

967 Holt-Oram Syndrome Associated with Combined Ostium Primum and Secundum Atrial Septal Defects: Successful Surgical Closure

HIROSHI MITSUOKA, SAJID CHUGHTAI, RENATO CUTARELLI, RAIS A. BEG, HOSSEIN NARAGHIPOUR and EARLE B. KAY

Ostium primum and ostium secundum atrial septal defects were successfully repaired in a 55 year old man with Holt-Oram syndrome and recurrent congestive heart failure.

969 Unilateral Pulmonary Vein Atresia: Diagnosis and Treatment

ANTOINE T. NASRALLAH, CHARLES E. MULLINS, DON SINGER, GUNYON HARRISON and DAN G. McNAMARA

Unilateral pulmonary vein atresia due to extensive intimal fibrosis of the pulmonary veins in a 16 month old boy was successfully treated by right pneumonectomy after angiocardiography made the definitive diagnosis revealing the lack of a site of entry for venous blood from the right lung into the circulation.

EDITORIALS

974 Metabolic Changes in Myocardial Infarction

RICHARD J. BING

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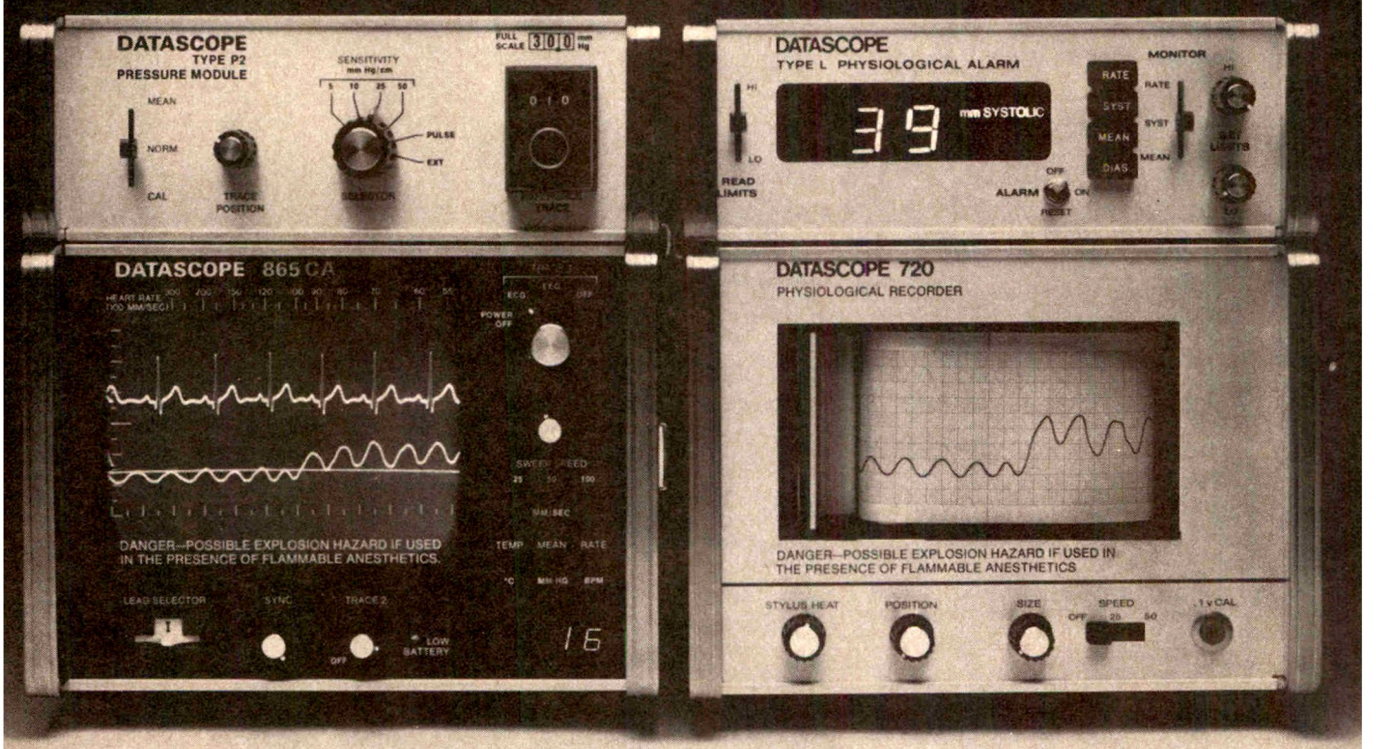

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975 **Problems in Measurement of Serum Digoxin by Commercially Available Radioimmunoassay Kits**
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CORRECTIONS

The left and right panels of Figure 1 on page 364 of the March issue were inadvertently transposed by the printer (Betriu A, Wigle ED, Felderhof CH, et al: Prolapse of the posterior leaflet of the mitral valve associated with secundum atrial septal defect. Am J Cardiol 35:363–375, 1975).

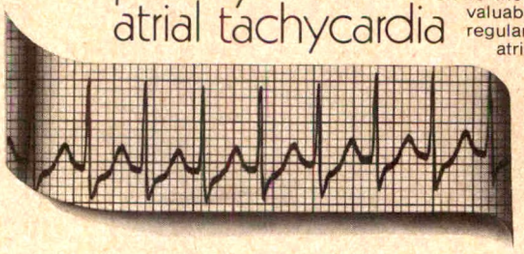
In Figure 2B on page 355 of the September issue, the left atrium was incorrectly labeled RA and thus the abbreviation was defined in the legend as right atrium (Hirschfeld SA, Emilson BB: Echocardiogram in calcified mitral anulus. Am J Cardiol 36:354–356, 1975).

in the inner circle o
Inderal® stands ou

The place of INDERAL (propranolol hydrochloride) among the standard drugs for the treatment of disturbed cardiac rhythm has been frequently reaffirmed throughout seven years of clinical use. In fact, after withdrawal of digitalis, "...it may be the treatment of choice for digitalis-induced arrhythmias, provided hypokalemia is not present."[1] It has been widely used in selected supraventricular arrhythmias that have proved resistant to digitalis and in tachyarrhythmias precipitated by exercise, emotional stress, or undesirable sympathetic stimulation; and it is also effective in controlling supraventricular tachyarrhythmias related to the Wolff-Parkinson-White syndrome.[2]

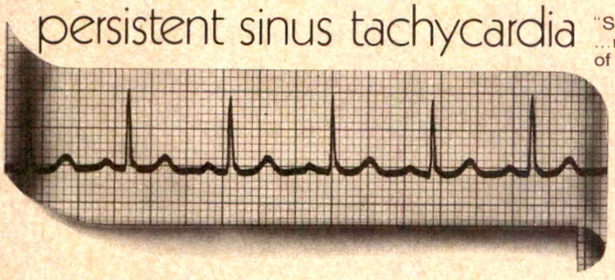
INDERAL protects the heart from undesirable catecholamine stimulation through its beta blocking action. Propranolol occupies the beta-receptor sites, making them unavailable to the beta-adrenergic stimulating effects of catecholamines. INDERAL is the first beta-adrenergic blocking agent in clinical cardiologic use.

paroxysmal atrial tachycardia



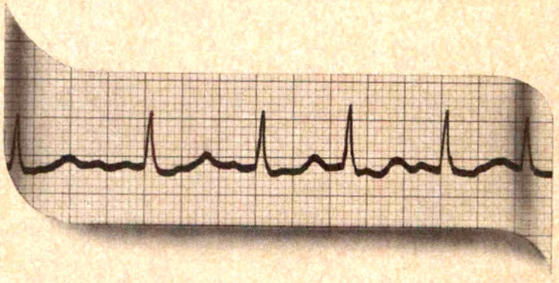
"In paroxysmal atrial tachycardia, the dru slows the ventricular rate, and also valuable in restoring the heart to regular sinus rhythm."[3] "Paroxysm atrial tachycardia induced by e ercise...has uniformly bee prevented by propranolol," ar results with INDERAL in th Wolff-Parkinson-White sy drome"...have been favorab in all but a few patients reporte This condition appears to b one of the more definite ind cations for propranolol."[4]

persistent sinus tachycardia



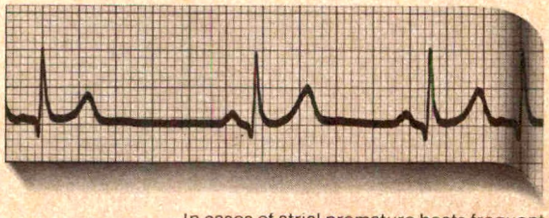
"Sinus tachycardia induced by stress ...may be inappropriate to the needs of the patient and, in fact, may be causing symptoms of itself. If the clinical situation does not suggest a needed compensatory sinus tachycardia and the heart rate is indeed inappropriate, treatment with propranolol has been successful."[4]

tachycardias and arrhythmias due to thyrotoxicosis



Although propranolol may accomplish only the reduction of the heart rate in hyperthyroidism, it has proved useful for this purpose. "Sinus tachycardia in hyperthyroidism which causes symptoms may be relieved by the administration of propranolol before definitive therapy....The author has observed that atrial fibrillation complicating hyperthyroidism was easily terminated using modest doses of propranolol."[4]

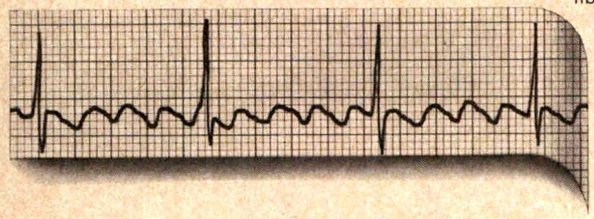
persistent atrial extrasystoles



In cases of atrial premature beats frequent enough that they could herald the onset of atrial fibrillation, it has been recommended that propranolol be used after other measures have failed to control the beats.[5]

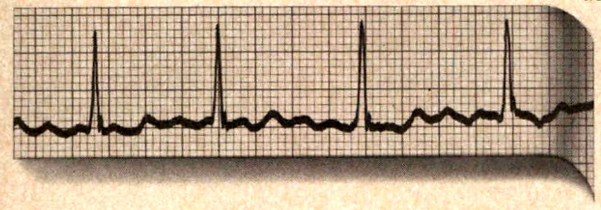
antiarrhythmia agents for supraventricular arrhythmias

atrial flutter



"In the presence of atrial flutter, ventricular rate is often difficult to control, and, as with an atrial fibrillation, propranolol hydrochloride should be added when the flutter is not controlled by digitalis, especially in the presence of mitral valve disease."[6]

atrial fibrillation

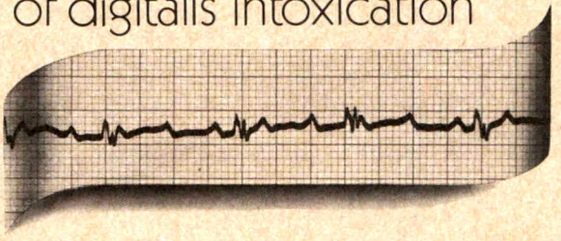


"One salutary effect of propranolol is slowing of the ventricular rate in atrial flutter and fibrillation."[4] In a review of the literature, it was noted that most patients with fibrillation not controlled by digitalis alone experienced slowing of the ventricular rate after administration of propranolol and a few reverted to sinus rhythm.[7]

---

and for tachyarrhythmias of digitalis intoxication

"Propranolol is very effective in treating arrhythmias caused by digitalis excess. Its use in this setting may be limited by the presence of significant congestive heart failure or heart block, both of which can be potentiated by propranolol. However, if given in small doses with careful monitoring, it is often of great value in the treatment of digitalis toxicity."[5]



References 1. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 2. Chung, E.K.: Postgrad. Med. *53*:107 (Apr.) 1973. 3. Harrison, D.C.: Clinical Guide to the Use of Beta-Adrenergic Blockade in Arrhythmias, Ayerst Laboratories, 1971, p. 10. 4. Reynolds, E.W.: Geriatrics *26*:150 (Feb.) 1971. 5. Helfant, R.H.: Med. Times *98*:118 (Jan.) 1970. 6. Sonnenblick, E.H.: Arrhythmias and Beta-Adrenergic Blockade, Ayerst Laboratories, 1971, p. 7. 7. Gibson, D., and Sowton, E.: Prog. Cardiovasc. Dis. *12*:16 (July) 1969.

Inderal®

Brand of propranolol hydrochloride

helps prevent or control catecholamine-induced cardiac arrhythmias

BETA-BLOCKADE/**INDERAL**®
(propranolol hydrochloride)

Ayerst

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BRIEF SUMMARY
(For full prescribing information, see package circular.)

Inderal®

Brand of
propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

INDICATIONS:

Cardiac Arrhythmias

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is non-compensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.
May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias
Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias
With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication
If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.) Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia.
Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis
INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma
After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL's opposite inotropic effect. The effect of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

When discontinuance of chronically administered INDERAL is planned, the dosage should be gradually reduced over a period of several weeks and the patient should continue to be carefully monitored. There have been reports of myocardial infarction occurring in angina pectoris patients following *abrupt* discontinuation of INDERAL therapy.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The oral route of administration is preferred.

ORAL

ARRHYTHMIAS—10-30 mg. three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg. three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg. daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg. administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg. (1 cc.) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED: BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride) TABLETS No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

INJECTABLE No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

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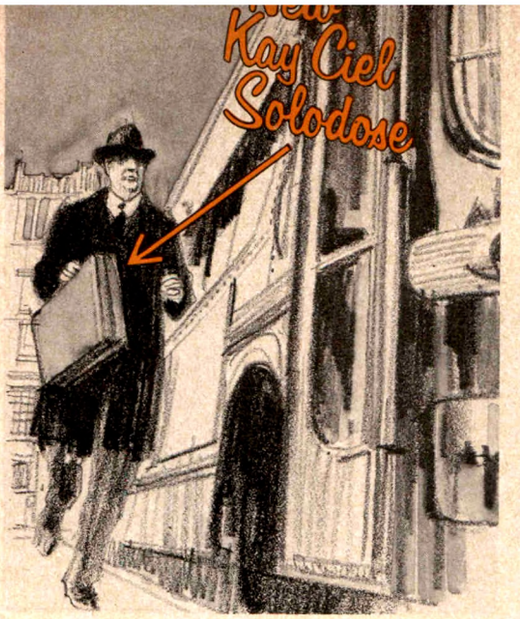

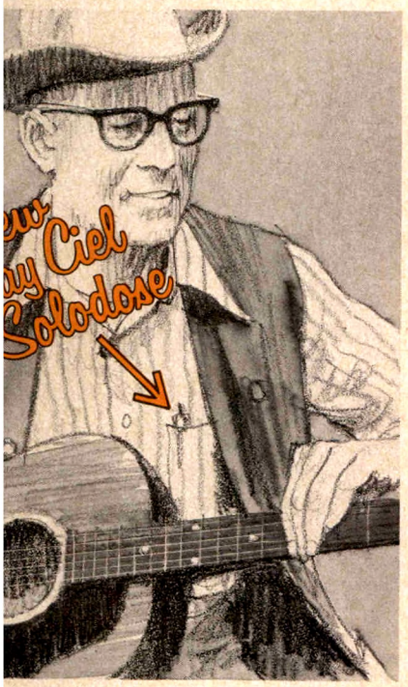

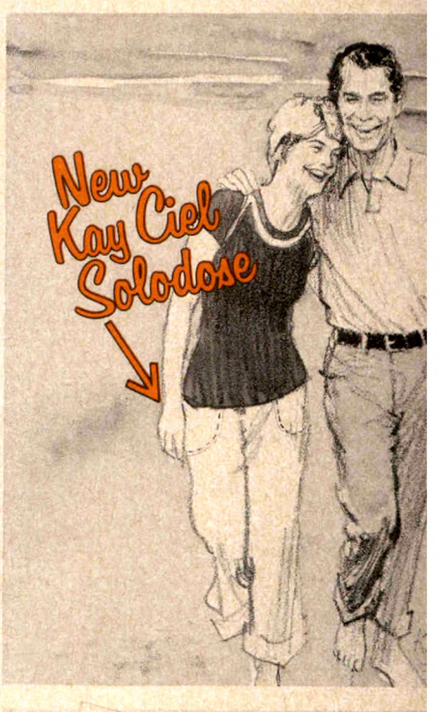

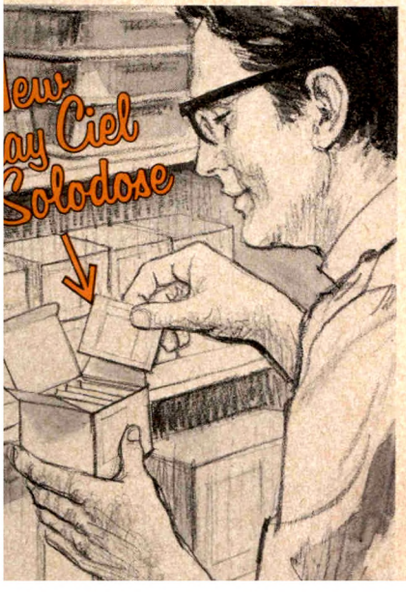

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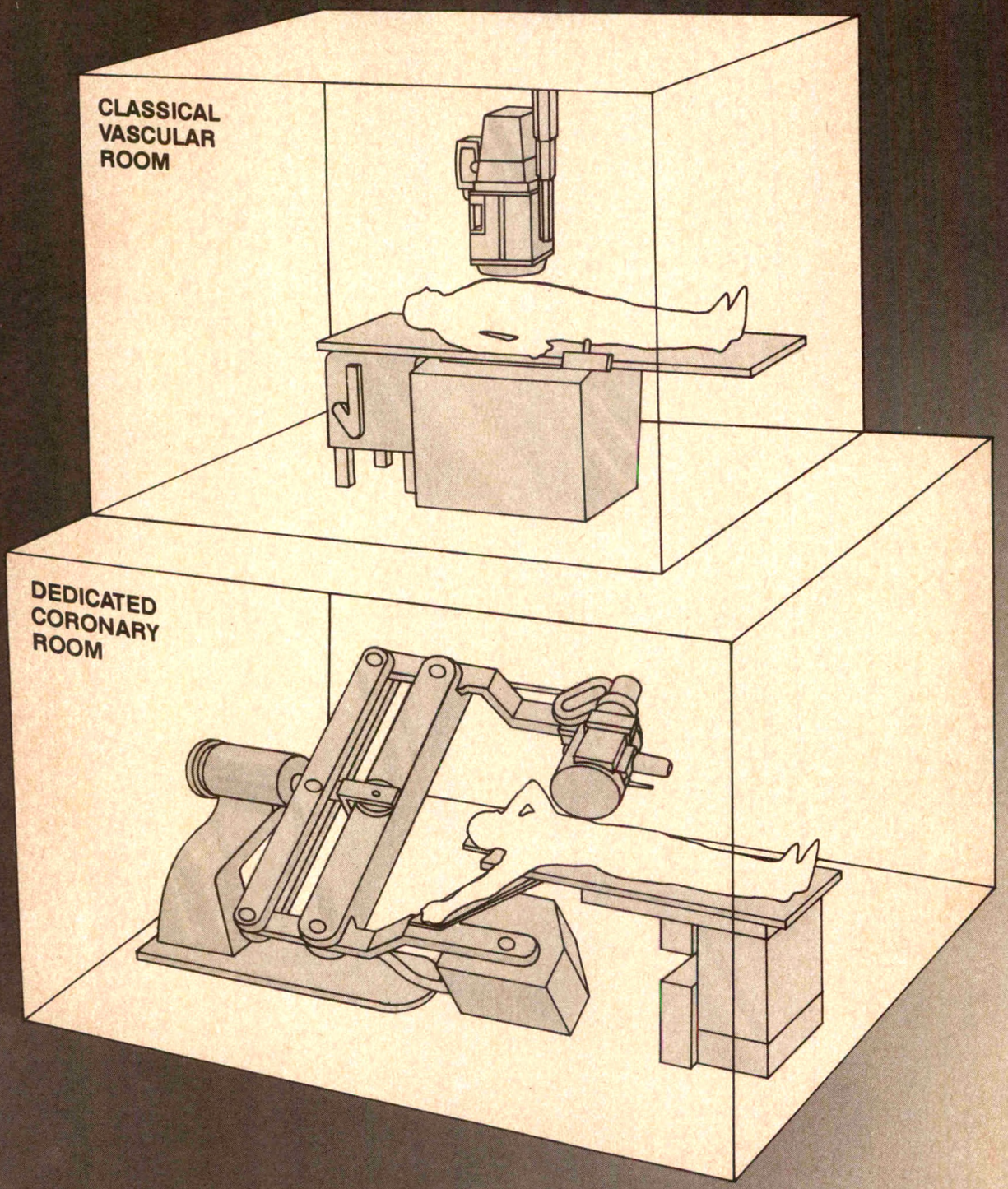
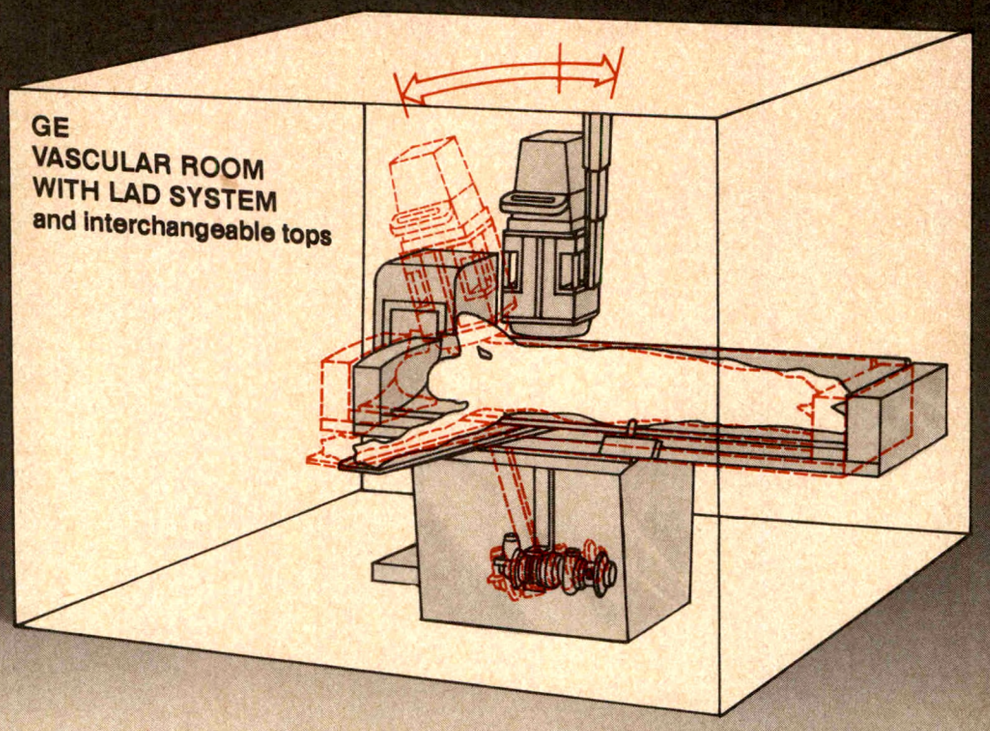


when one does it all?



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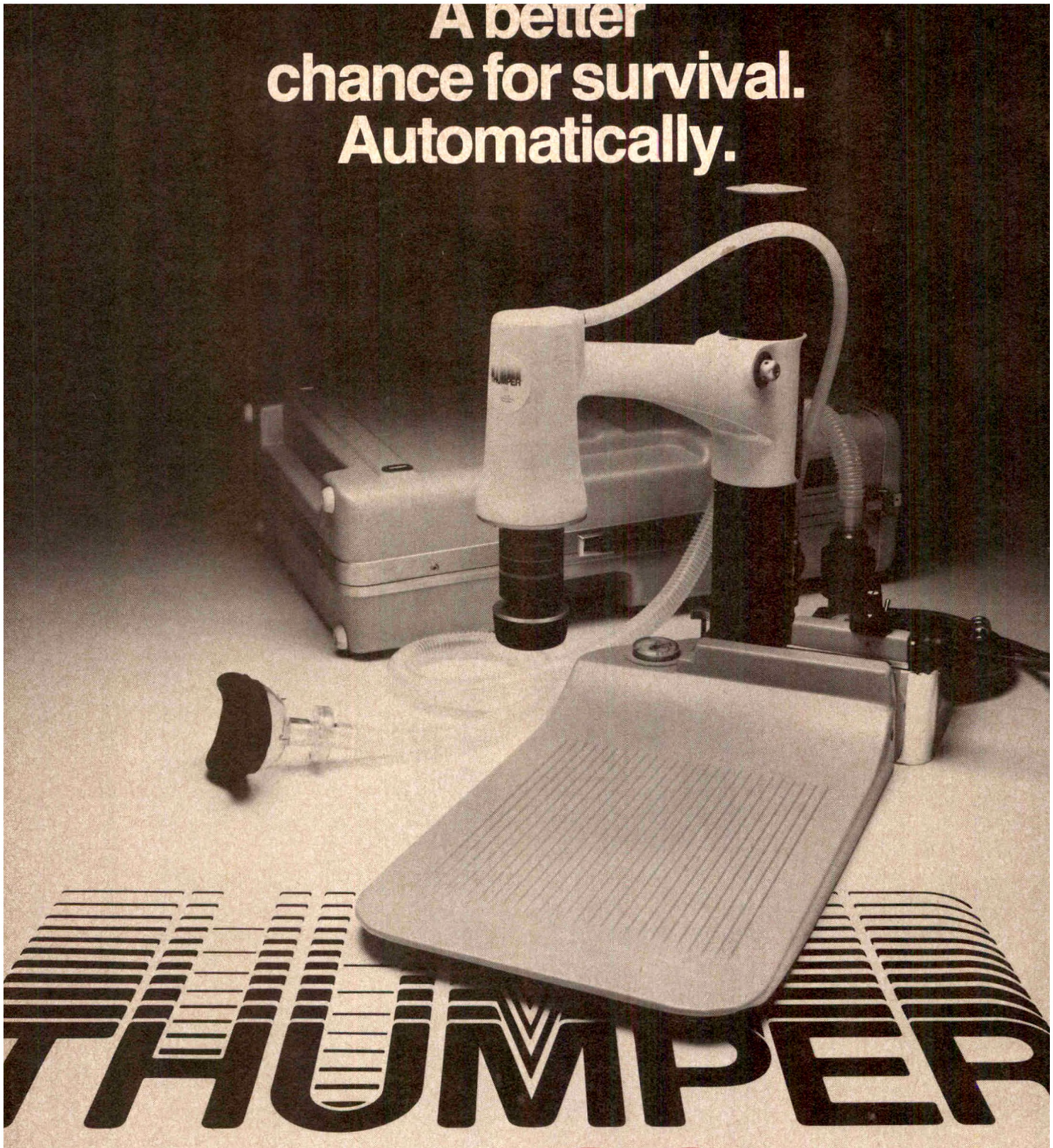

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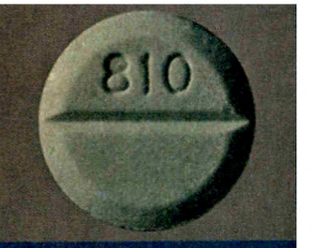

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- ☐ acts just as fast for therapeutic use...within 2 minutes
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- ☐ helps dissolve medication more easily
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SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals. Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS
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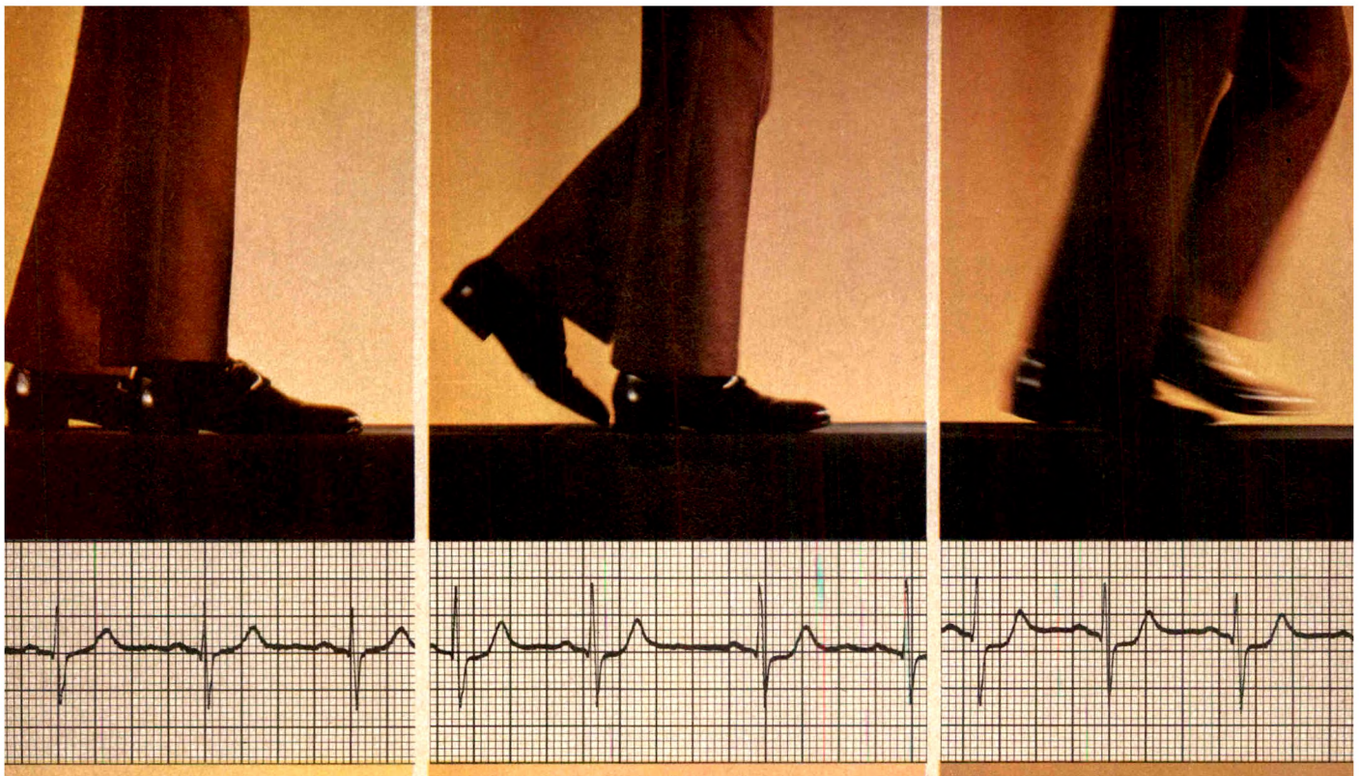
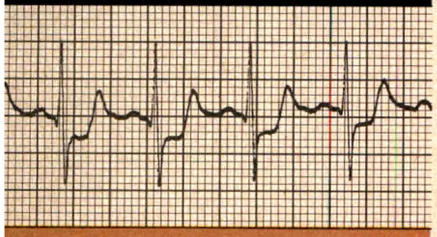


nding, at rest, V-5, HR-74. nerican's Stress Test Electrode pplies immediate base line stability. sting with a narrow, drift free base e can begin as soon as the self- nering, silver/silver chloride elec- des have been applied to the patient l connections made to your nitoring equipment.

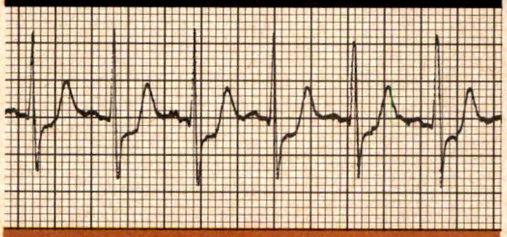
4th Minute at 2 mph, 0% Grade, V-5, HR-75. Base line stability is maintained because of the electrode's gel retaining cup and gel impregnated foam pad; the gel pad is slightly oversize to assure positive, continuous pressure at the electrode-skin interface. The result: virtual elimination of base line instability and motion artifact.

4th Minute at 3 mph (8th minute test), 0% Grade, V-5, HR-83. (T patient's ECG indicates 1 mm of depression.) Fully shielded cable and leadwire provide an effective barrier to the electrical interference that might otherwise mask small amounts of S-T depression.

Do your stress test ECGs show everything you need to see?

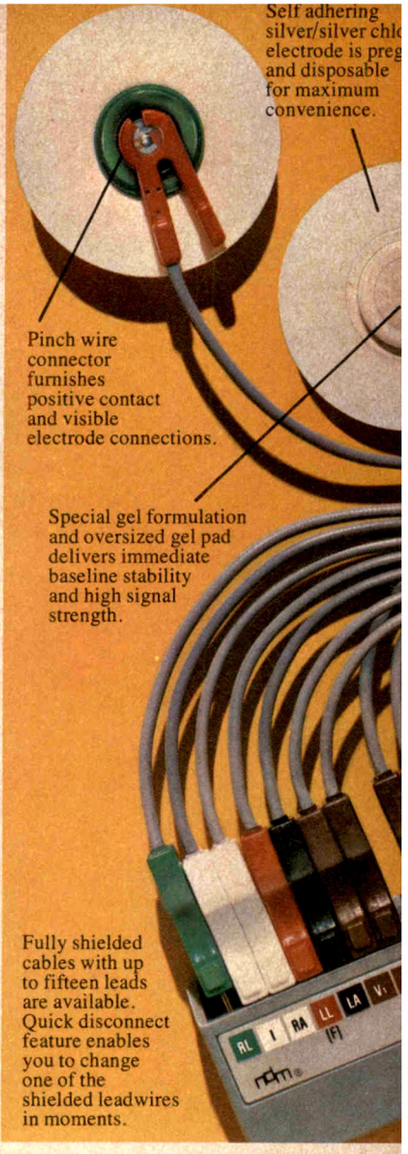


1 Minute at 3 mph (12th minute test), 5% Grade, V-5, HR-117. T depression increases to 2.5 mm.) en at high work loads, the Ameri- Stress Test Electrode and fully elded cable system delivers a stable se line and noise-free signal.



4th Minute at 3 mph (16th minute of test), 7.5% Grade, V-5, HR-135. (S-T depression drops to 2.0 mm.) Long test procedures seldom affect the electrode's contact with a patient's skin; trace quality remains high, even with patients who perspire heavily.

(Because of this electrode's special gel formulation, application periods of longer than four hours are not recommended.)



Compare the stress test electrocardiograms you have been getting with those reproduced above.* There's a reason for the unusually high quality of the ECG traces shown: The patient was being monitored with American's Stress Test Electrode and fully shielded cable system.

If you've been diagnosing from stress test electrocardiograms that display wide or unstable base lines, severe motion artifact or possible hidden S-T depression, please contact us. We think we can help.

*Examples shown were produced under clinical conditions during an actual stress test procedure using the American Stress Test Electrode system.

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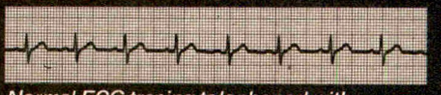

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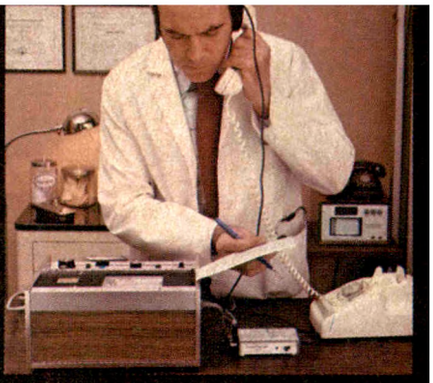

You can immediately receive the telephoned data as a series of audible "beeps" indicating each QRS complex or pacemaker spike. To receive a permanent record of ECG or pacemaker artifact, just connect a CardioBeeper® ECG Decoder to your telephone and to any conventional ECG machine. Or instead, connect a CardioBeeper® Decodalyzer to your phone to obtain a visual readout of heart rate or pacemaker rate in BPM, interval count in msec. or a direct ECG tracing for your records.

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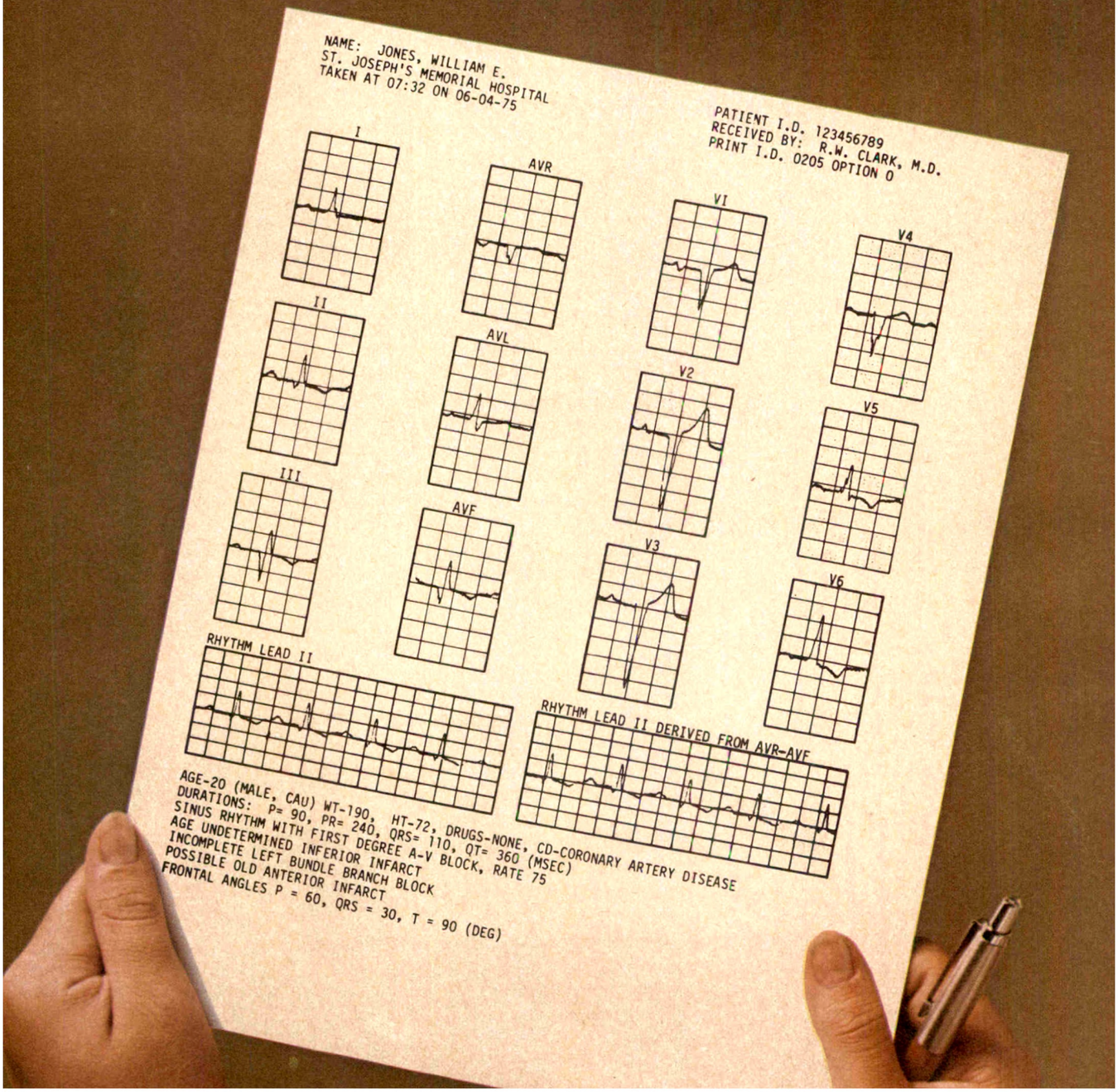

DECEMBER 197

The American Journal of CARDIOLOGY

VOLUME 3

NUMBER

CLINICAL STUDIES

Electrophysiologic Studies in the Denervated Transplanted Human Heart

II. Response to Norepinephrine, Isoproterenol and Propranolol

DAVID S. CANNOM, MD*
ALAN K. RIDER, MD
EDWARD B. STINSON, MD
DONALD C. HARRISON, MD, FACC

Stanford, California

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From The Cardiology Division and the Department of Cardiovascular Surgery, Stanford University School of Medicine, Stanford, Calif. 94305. This work was supported in part by Grants HL-5866, HL-13108, HL-08696, and Program Project Grant NIH 1-PO1-HL-15833 from the National Institutes of Health, Bethesda, Md.
Manuscript accepted March 7, 1975.

* Present address: Yale New Haven Hospital, 333 Cedar St., New Haven, Conn. 06510.

Address for reprints: Donald C. Harrison, MD, Cardiology Division, Stanford University School of Medicine, Stanford, Calif. 94305.

Five patients who had received a transplanted human heart 1 to years previously were studied to determine the effects of norepineph rine, isoproterenol and propranolol on the atrioventricular (A-V) con duction system. Using the His bundle technique, atrial, His bundle an ventricular electrograms were recorded, and central aortic pressur was monitored during the administration of these drugs. Norepineph rine was given by continuous infusion to four patients in doses rangin from 4 to 8 μg/min, with the systolic arterial pressure increasing by a average of 72 mm Hg. Concomitantly, there was an average increas in the rate of the donor atrium of 32 beats/min, and a reflex slowing o the recipient atrium of 23 beats/min. The A-H interval shortened by a average of 27 msec. Isoproterenol dose-response curves were per formed in three patients, with the maximal dose being 5.2 μg by intra venous bolus infusion. The rate of the donor atrium increased by an av erage of 40 beats/min, and that of the recipient atrium by 18 beats min. The A-H time shortened by an average of 25 msec, with a drop i systolic blood pressure averaging 23 mm Hg. Propranolol (7 mg intra venously) was given to three patients and the peak doses of norepi nephrine and isoproterenol were again infused. Beta adrenergic block ade was achieved at this dose of propranolol since there was only a minimal increase in the donor atrial rate after infusion of the drug. The A-H interval was not altered by catecholamine infusion after achieve ment of beta blockade. However, the levels of systolic hypertensio noted after infusion of norepinephrine were not altered by propranolol The denervated transplanted human heart appears to respond normally to norepinephrine and isoproterenol, and the electrophysiologic effects of these agents are blocked by propranolol.

Extensive investigative work in the denervated canine model has demonstrated the presence of the alpha and beta cardiovascular re ceptors. Although the autonomic nervous system is important in cardi ac performance, this work is the first validation in man that (1) the functional integrity of the beta receptor is maintained even when the autonomic nerves are absent, and (2) the intrinsic properties of the sinus and atrioventricular nodes are the keystone in stabilizing cardiac electrophysiology after denervation.

In the past 25 years the availability of adrenergic and cholinergic agonists and antagonists has made it possible to construct a conceptual model of the function of the autonomic nervous system. Specific receptor sites are defined functionally, and the effect of any drug, whether alpha or beta adrenergic, on the autonomic nervous system is commonly discussed among basic scientists and medical house officers. Our cardiac transplantation program provides a unique opportunity for electrophysiologic study of the autonomic nervous system in the denervated, transplanted human heart. The purposes of our study were threefold: (1) to describe in detail the effects of norepinephrine, isoproterenol and propranolol on atrioventricular (A-V) conduction in the denervated human heart; (2) to detail experimentally the effects of beta adrenergic blockade on conduction in the denervated human heart, and (3), using these data, to extend understanding of the functional characteristics of the beta receptor at both the sinus and A-V nodes. The experimental model employed provides the opportunity of separating the effects of the autonomic nerves, as such, from those of the receptor site itself.

Methods

The five patients described had received a transplanted human heart at Stanford University Medical Center 1 to 3 years previously and were admitted at this time as part of an on-going evaluation of this patient population. All were well clinically at the time of study and were considered to be in New York Heart Association functional class I. All were receiving orally administered azathioprine and prednisone, but none was taking any medication known to alter the characteristics of the A-V conduction system.

Each patient underwent routine left and right heart catheterization and coronary arteriography, with normal results in each case, on the day before the electrophysiologic studies to be described.

The patients were brought to the catheterization laboratory in the nonsedated, postabsorptive state, having received systemic antibiotic agents (penicillin and methacillin) the night before and the day of study. The voluntary nature of the study was explained to each patient, and informed consent obtained.

Instrumentation

Instrumentation was performed in a similar manner for each patient. A tripolar catheter was inserted into the right femoral vein and, by methods previously described,[1] advanced to a position to record the His bundle and ventricular electrograms. A no. 7F quadrupolar catheter was inserted percutaneously into the left femoral or right internal jugular vein and advanced to a position in the left atrium, with use of a counterclockwise loop, so that the two distal poles of this catheter were high in the right atrium. In this way it was possible to record electrograms from both the recipient atrium (A_R) and the donor atrium (A_D). The surgical procedure used during transplantation, which results in two functioning atria (A_D and A_R) and two sinus nodes, has previously been described in detail.[2] A no. 5.2F Cook pigtail catheter was inserted into the right femoral artery and advanced to a position in the central aorta below the diaphragm, allowing measurement of central aortic pressure.

The two proximal terminals of the atrial catheter and the His bundle electrogram were transmitted to the alternating current input of an electrocardiographic amplifier, with the filter frequencies set between 40 and 500 hertz. Standard lead II was recorded simultaneously. The central aortic catheter was attached to a Statham transducer, and all signals were simultaneously displayed on a switched beam Electronics for Medicine oscilloscope and recorded on photographic paper at a paper speed of 100 mm/sec. A peripheral intravenous infusion using dextrose in water was begun in a forearm, to allow administration of drugs during the study.

Electrophysiologic Studies

Stable recordings were made of the recipient atrium, donor atrium, His bundle and ventricular electrograms in each case. The two distal terminals of the quadripolar catheter were attached to a battery-powered pacemaker (Medtronics 5837) and right atrial pacing, using a 2 msec impulse twice diastolic threshold, was used to validate the His potential. Initial control measurements were then made of the cycle length of the recipient and donor atria, the atrium to His bundle conduction interval (A-H time) and the His bundle to ventricular conduction interval (H-V time). Standard definitions were used for measurement of these intervals.

Norepinephrine: After the recording of control intervals, various drugs were administered to the five patients. Four patients (Cases 1, 3, 4 and 5) initially received an infusion of norepinephrine. This infusion was begun at a rate of 1 μg/min intravenously and was continued until the systolic arterial pressure had risen by 55 to 85 mm Hg. The infusion rate was increased by increments of 1 μg/min and was held at each level for 5 minutes while determinations were made of the aortic pressure as well as the rates of the donor and recipient atria and the A-H and H-V times. The level of norepinephrine yielding peak response was recorded for each patient.

Isoproterenol: Infusion of norepinephrine was terminated and time allowed for all variables to return to control levels (averaging 20 to 25 minutes per patient). Isoproterenol dose-response curves were performed after the norepinephrine infusion in Patients 3 and 5 and were performed initially in Patient 2, who did not receive norepinephrine. Standard technique was employed, using a rapid intravenous bolus injection of isoproterenol over a 10 second period and then measuring, for the next 5 minutes, the aortic pressure, the recipient and donor atrial rates and the A-H and H-V intervals. The initial dose was 0.35 μg, followed by 0.7, 1.75 and 3.75 μg. The intent of these injections was to increase the rate of the donor atrium by approximately 40 beats/min, which was typically achieved using 3.75 μg in Patients 2 and 5, whereas Patient 3 required 5.2 μg as a bolus injection. Again, the level of drug resulting in peak response was noted for each patient.

Propranolol: Control conditions were allowed to return (10 to 12 minutes) and in those patients having a complete study (Cases 2, 3 and 5), 7 mg of propranolol was administered intravenously over 10 minutes. Measurements of the previously listed variables were made every minute. Five minutes after the infusion of propranolol was concluded (or 15 minutes after it was begun), the effects of beta adrenergic blockade were assessed. The dose of norepinephrine or isoproterenol, or both, resulting in the peak response before the administration of propranolol was administered again in a fashion similar to that of the initial drug administrations. For norepinephrine, the drug was given as an intravenous drip infusion at a rate of 8 μg/min in Patients 3

to 5, with monitoring every minute of the recipient and donor atria, the blood pressure and the A-H and H-V intervals. When the effect of the norepinephrine infusion had abated, as judged by return to postpropranolol arterial blood pressure levels, the dose of isoproterenol yielding the peak response before administration of propranolol was again given to Patients 2, 3 and 5. Again the recipient and donor atrial rates, the central aortic blood pressure and the A-H and H-V intervals were measured each minute for 10 minutes.

Amyl nitrate and atropine: To document denervation, amyl nitrate was given by inhalation, while blood pressure and heart rate were monitored. In each instance a decrease of at least 20 mm Hg in systolic pressure was accomplished without any measurable increase in heart rate. After pressure and heart rate had returned to control values, 2 mg of atropine was administered intravenously, with several measurements of heart rate and the A-H interval. As in previous studies from our laboratory,[2] no increase in heart rate or decrease in A-H intervals was detected. The patients tolerated the procedure well, and no adverse effects of these prolonged procedures were noted.

Results

Control Data

Table I summarizes the electrophysiologic data obtained in the five patients before any pharmacologic interventions were undertaken. The typical acceleration of the donor atrial rate in relation to the rate of the recipient atrium is noted in all but Patient 3. The recipient atrial rate of this patient was 143 beats/min and was not altered by any of the pharmacologic agents administered (see Discussion). The control A-H and H-V intervals were normal for this laboratory. The blood pressure of all five patients, as measured by the systemic arterial catheter, was within the normal range.

Effects of Norepinephrine

The characteristic result of administration of norepinephrine in four patients was an average increase of 72 mm Hg in systolic blood pressure with a concomitant average increase of 32 beats/min in donor atrial rate (Table IIA). The recipient atrial rate, on the other hand, slowed by an average of 23 beats/min, although no change was noted in Patient 3, whose recipient atrial rate continued to be 143 beats/min. There was a shortening of the A-H interval by an average of 27 msec, whereas the H-V interval did not change. The dose of drug required to achieve the desired increase in arterial blood pressure was 4 μg/min in Patient 1 and 8 μg/min in Patients 3, 4 and 5 (Fig. 1). The values shown are after the drug had been administered at that level for 10 minutes. The donor atrial rate increased in a manner parallel to changes in arterial blood pressure and did not suggest hypersensitivity, defined as lowered threshold of the denervated heart to exogenous catecholamines.

Effects of Isoproterenol

Isoproterenol dose-response curves were performed in Patients 2, 3 and 5. A typical response is shown in Figure 2, and the data for the three patients

TABLE I

Control Electrophysiologic Data

Case no.	A_R (per min)	A_D (per min)	AH (msec)	HV (msec)	BP (mm Hg)
1	70	88	120	50	130/80
2	60	110	100	50	115/90
3	143	100	120	30	120/80
4	86	100	100	50	110/70
5	85	103	95	50	130/90

A_D = donor atrial rate; A_R = recipient atrial rate; BP = blood pressure.

TABLE II

Electrophysiologic Data After Pharmacologic Interventions

Case no.	Dose* (μg)	A_R (beats/min)	A_D (beats/min)	AH (msec)	HV (msec)	BP (systolic mm Hg)
A. Effects of Norepinephrine						
1	4	↓6	↑16	↓40	NC	↑72
3	8	NC	↑48	↓20	NC	↑55
4	8	↓11	↑25	↓40	NC	↑80
5	8	↓52	↑38	↓10	NC	↑80
Average change		↓23	↑32	↓27	NC	↑72
B. Effects of Isoproterenol						
2	3.5†	↑20	↑38	↓20	NC	↓15
3	5.2	NC	↑41	↓20	NC	↓35
5	3.75	↑16	↑42	↓35	NC	↓20
Average change		↑18	↑40	↓25	NC	↓23
C. Effects of Propranolol, Intravenously						
2	7 mg	↓3	↓12	↑10	NC	NC
3	7 mg	NC	↓23	↑20	NC	NC
5	7 mg	↓21	↓23	↑15	NC	↓10
D. Effects of Beta-Adrenergic Blockade						
2	I, 3.5	↑3	↑5	NC	NC	NC
3	NE, 8	NC	↑13	NC	NC	↑80
	I, 5.2	NC	NC	NC	NC	NC
5	NE, 8	↓37	↑5	NC	NC	↑80
	I, 3.75	↑8	↑5	NC	NC	NC

* Dose of drug giving peak response.
† Largest dose given using intravenous bolus injection.
↓ = decreased; ↑ = increased; I = isoproterenol; NC = no change; NE = norepinephrine; other abbreviations as in Table I.

are summarized in Table IIB. The response observed after 30 seconds to 1 minute at the highest level of isoproterenol given is listed. A characteristic rise in both the donor and recipient atrial rate is noted, with the magnitude of the rate of rise of the donor atrial rate exceeding that of the recipient atrial rate. Again Patient 3 showed no alteration of the recipient atrial rate during the administration of isoproterenol. A substantial decrease in the A-H interval is again noted, whereas the H-V interval remained constant in each case. Moderate decreases in the systolic blood pressure were observed in each case.

Effects of Propranolol

The electrophysiologic data for the three patients (Cases 2, 3 and 5) 5 minutes after the infusion of 7 mg of propranolol over 10 minutes are summarized in

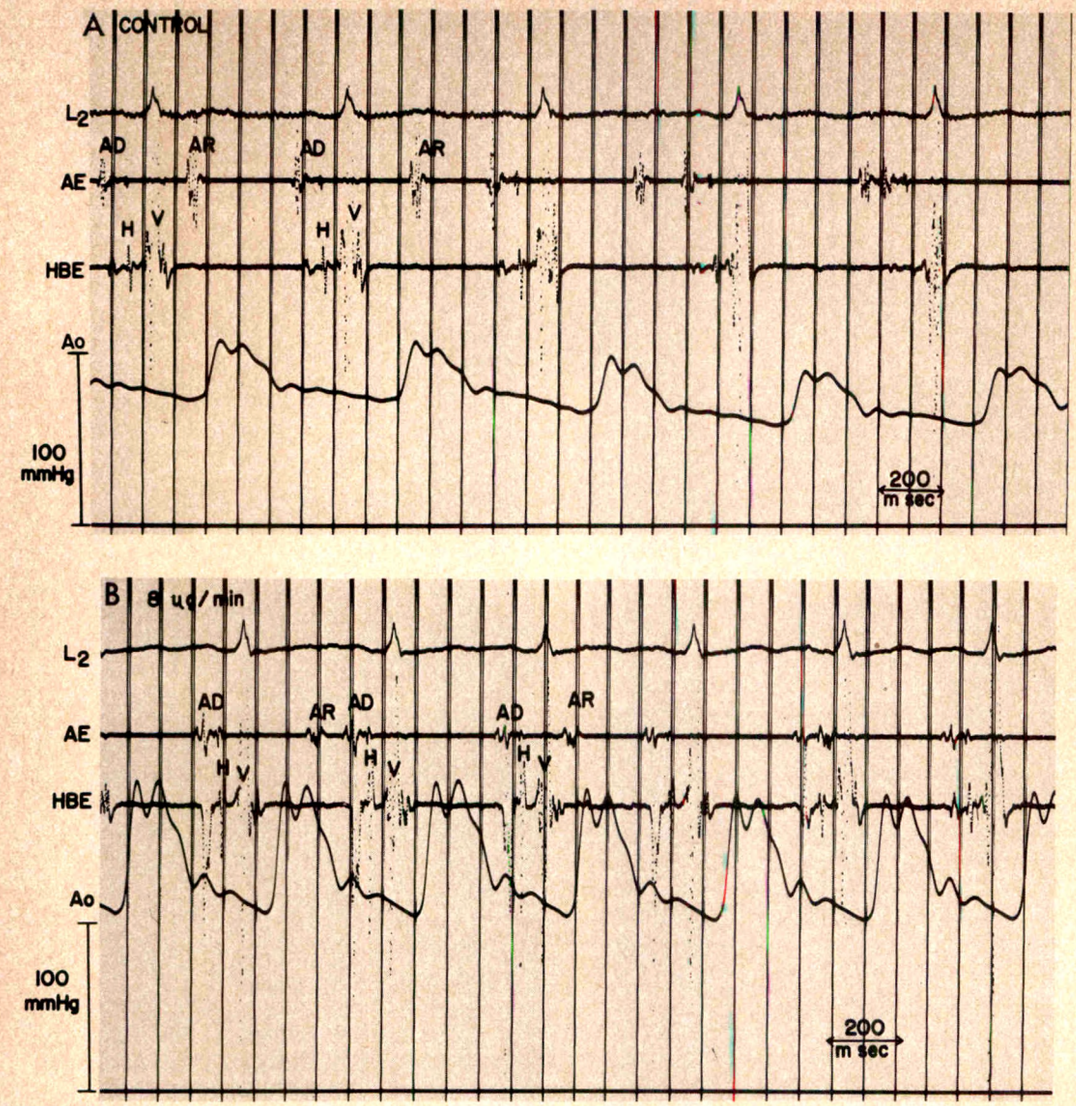

FIGURE 1. Case 4. Response to infusion of norepinephrine. **A**, control tracing: The patient's state prior to the infusion of norepinephrine. **B**, data recorded after the patient had received 8 µg/min of norepinephrine for 10 minutes. The blood pressure has increased from 110/70 in the control state to 190/100 after norepinephrine infusion. The donor sinus nodal rate has increased from 100 to 125 beats/min, whereas the recipient atrial rate has decreased from 86 to 75 beats/min. The A-H time has shortened from 100 msec in the control state to 60 msec, with no change noted in the H-V time. AD = donor atrium; AE = high atrial electrogram; Ao = central aortic pressure; AR = recipient atrium; H = His bundle potential; HBE = His bundle electrogram; L_2 = electrocardiographic lead II; V = ventricular electrogram. Time lines are 100 msec apart; paper speed is 100 mm/sec. The values for the various intervals in this figure can be found in Table I.

Table IIC, and a typical response is shown in Figure 3. A characteristic diminution in the rate of both the donor and recipient atria was seen, with an increase in the A-H interval averaging 15 msec. No change was seen in the duration of the H-V interval and the blood pressure fluctuated little, if any, after the administration of propranolol.

Table IID summarizes the effects of beta adrenergic blockade in those patients (Cases 2, 3 and 5) who received adrenergic stimulating agents after the establishment of beta blockade. Each patient received the level of adrenergic agonist that had given a maximal response before the intravenous administration of propranolol. Patient 2 received only isoproterenol after beta blockade, whereas Patients 3 and 5 had received both norepinephrine and isoproterenol. Of note are the trivial increases in the rate of the donor atrium after the administration of both drugs. Small increases were observed in the rate of the recipient atrium in Patients 2 and 5 after administration of isoproterenol; there was no change in the recipient atrial rate of Patient 3 after administration of either drug.

Whereas both drugs had previously shortened the A-H interval, this effect was ablated after propranolol. There was no change in the H-V interval. The peripheral effects of norepinephrine were unaltered as the systolic blood pressure increased by 80 mm Hg in

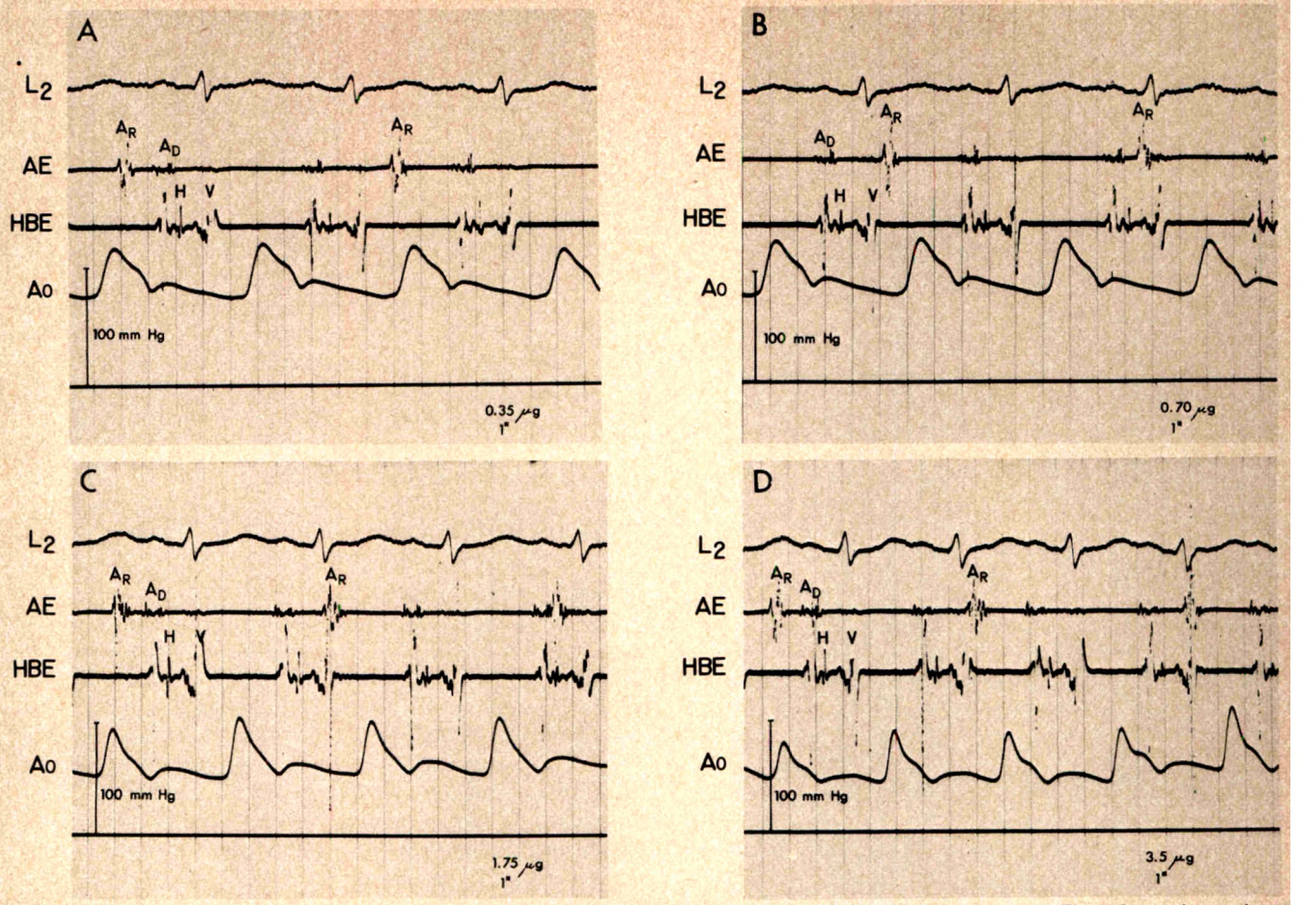

FIGURE 2. Case 3. Isoproterenol dose-response curve. **A**, 1 minute after bolus infusion of 0.35 μg of isoproterenol. There is no change in any variable from the patient's control electrophysiologic and hemodynamic state. **B**, 1 minute after infusion of 0.7 μg of isoproterenol. Again, no changes from the control state are noted. **C**, 1 minute after injection of 1.75 μg of isoproterenol. The central arterial blood pressure has decreased from 115/90 mm Hg in the prior tracings to 100/50. The recipient atrial rate has increased from 60 to 77 beats/min, whereas the donor atrial rate has increased from 110 to 125 beats/min. The A-H interval has shortened from 100 to 80 msec; the H-V interval remains unchanged. **D**, 1 minute after intravenous injection of 3.5 μg of isoproterenol. The arterial blood pressure is now 90/50 mm Hg. The donor atrial rate is 14[illegible] beats/min, the recipient atrial rate 80 beats/min. This response was considered a maximal effect for Patient 2, and this dose was used after beta blockade had been achieved (see Fig. 4). Abbreviations as in Figure 1.

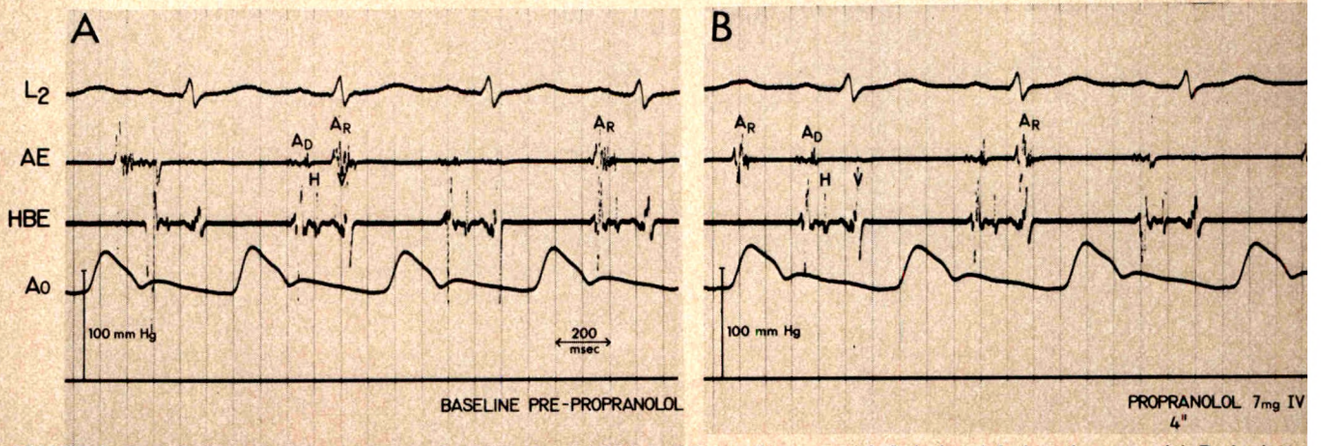

FIGURE 3. Case 2. Characteristic response after intravenous infusion of 7 mg of propranolol. **A**, before infusion of propranolol. **B**, 4 minutes after intravenous administration of 7 mg of propranolol. There are no changes in central arterial blood pressure, but the donor atrial rate has slowed by 12 beats/min and the recipient atrial rate by 3 beats/min. The A-H interval is prolonged by 10 msec, and no change is noted in the H-V interval. Abbreviations as in Figure 1.

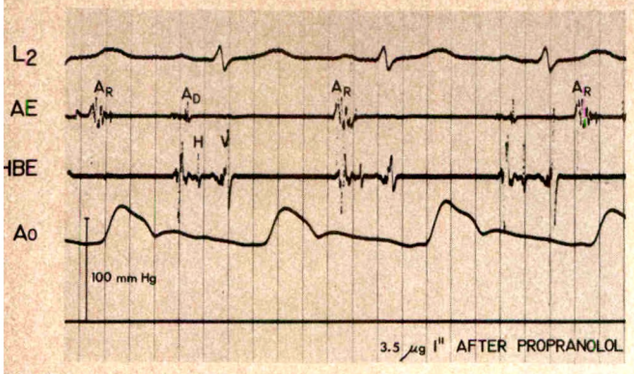

FIGURE 4. Case 2. The response to isoproterenol after intravenous administration of 7 mg of propranolol. This tracing was taken 1 minute after the bolus injection of 3.5 μg of isoproterenol. The results can be compared with those in Figure 3B, which was recorded only shortly before the isoproterenol reinfusion. Of note is the insignificant increase in the donor atrial rate (5 beats/min) and in the recipient atrial rate (3 beats/min) without accompanying alterations in the A-H or H-V intervals. The arterial blood pressure remains unchanged. Abbreviations as in Figure 1.

Patients 3 and 5. Figure 4 shows a characteristic response to infusion of isoproterenol 15 minutes after administration of propranolol.

Atropine and Amyl Nitrate

Administration of 2 mg of atropine after the cessation of the previous studies resulted in changes comparable with those we[2] have previously reported. There was no alteration of the donor atrial rate, whereas the recipient atrial rate increased by an average of 25 beats/min. Subsequent administration of amyl nitrate by inhalation produced only small increases (average 5 beats/min) in heart rate, with a concomitant reduction in mean arterial pressure documenting adrenergic denervation. In our experience,[2] such results have been a constant feature of the denervated human transplanted heart, without any evidence for reinnervation.

Discussion

These electrophysiologic studies help to clarify the intrinsic effects of norepinephrine and isoproterenol on the human A-V conduction system. In addition, they help to define the characteristics of the adrenergic receptor in the absence of autonomic nerve endings.

The initial work of Langley[3] and Ahlquist[4] used the model of the alpha and beta adrenergic receptors as a conceptual framework within which to understand the effects of various sympathomimetic amines. Recently it has been suggested that a biochemical definition of these receptors in various organ systems is possible, although these findings remain controversial.[5] Our data permit speculation regarding the effect of the autonomic nerves on the function of these receptors and the functional effect of stimulation of the beta receptor on the conduction system.

The basic electrophysiologic data presented in Table I confirm our earlier work,[2] again suggesting that in the transplanted human heart the conduction rates measured, including the A-H and H-V times, are virtually identical to those obtained in the normal nondenervated heart. However, we observed that the donor sinus node (which controls the intrinsic ventricular rate of the transplanted heart) is faster at rest than the sinus node of the normal human heart. This observation is consistent with the concept that cholinergic influences predominate at the sinus node at rest and, with the removal of all autonomic tone of the donor heart after transplantation, the intrinsic rate of the sinus node increases.[2]

Effects of alpha and beta receptor stimulation (norepinephrine): Norepinephrine is known to stimulate both alpha and beta receptors,[6] and its infusion in four patients in this study (Table IIA) confirms that its effects in the denervated heart are similar to those in the normal heart. Rather large doses were given to increase the systolic blood pressure by 50 to 80 mm Hg. As the blood pressure rose to these levels, the carotid baroreceptors were stimulated and, in three of four patients the still innervated recipient atrium reduced its intrinsic rate by an average of 23 beats/min. This would be the expected result for the recipient atrium, which is still controlled by the baroreceptor mechanisms. Of particular importance is the acceleration in rate of the donor atrium, which is not innervated and on which baroreceptor mechanisms are therefore not operant. This increase is due to the direct action of norepinephrine on the sinus node.

At infusion rates of 4 to 8 μg/min, the overall average increase in the rate of the donor atrium was only 32 beats/min. Although prior studies in dogs[7,8] have shown hypersensitivity of the denervated heart to norepinephrine, we cannot determine if our rate increase was disproportionate. In previously cited work, absolute values for increases in heart rate were not given; however, our observations suggest that a hypersensitive response to the administration of norepinephrine at drug doses that are generally used clinically was minimal, if present. Our observations were not controlled, however, and caution should be exercised in their interpretation. Several reasons for variance with previous work with dogs can be discussed. First, Willman et al.[9] observed that in dogs the hypersensitivity of the denervated heart recedes with the demonstration of reinnervation. We have no evidence to suggest that the hearts of our study patients were autonomically reinnervated and, thus, we cannot invoke this hypothesis to explain the absence of hyperactivity due to catecholamine infusion in our patients. Second, there may be a species difference in the hypersensitive responses or in the response to norepinephrine. Hypersensitivity is frequently more easily demonstrated by a change in threshold to small amounts of norepinephrine. We did not use these small doses. Third, perhaps the delivery of the pharmacologic agent to the receptor is different after rejection episodes in the human heart. Fourth, since

by all known pharmacologic mechanisms hypersensitivity should occur, it is possible that we did not perform the correct experiments. Perhaps the infused norepinephrine was rapidly taken up by other adrenergic nerve endings in the body that were not altered by cardiac transplantation.

The A-H time, a measure of A-V nodal conduction time, was shortened in our study patients by an average of 27 msec, demonstrating that norepinephrine has a direct effect on the refractoriness of A-V nodal conduction independent of autonomic innervation. The H-V interval did not change in any of the four patients studied. This observation is consistent with recent work in dogs, which demonstrated that the bundle branches are unresponsive to either beta adrenergic stimulation or blockade.[10]

Effects of beta receptor stimulation (isoproterenol): Isoproterenol alone has been shown to be a direct beta stimulator.[6] Isoproterenol dose-response curves were obtained in three patients, and a response in terms of the chronotropic effect of isoproterenol was comparable with that seen in normal subjects[11] and in the few studies previously performed in the transplanted human heart.[12,13] As in the study of Carleton et al.,[13] the response of the donor sinus nodal rate was greater than that of the recipient sinus nodal rate even though the initial rate of the sinus node of the donor heart was faster than that of the recipient.

A shortening of the A-H interval comparable with that observed in the norepinephrine studies was seen with the infusion of isoproterenol, thus demonstrating a direct decrease in refractoriness at the A-V node. Autonomic influence does not modify this direct effect, which is similar to that seen in the innervated human heart.[14] Modest decreases in the peripheral blood pressure were noted with infusion of isoproterenol.

Effects of beta receptor blockade (propranolol): The infusion of 7 mg of propranolol over 10 minutes gave results comparable with those seen in the normal heart.[15] Both the recipient and donor atria showed a slowing in their intrinsic rate compatible with a direct effect of propranolol at the sinus node. Likewise, the A-H time increased as A-V nodal refractoriness increased. The H-V interval did not change, and only minimal changes were noted in blood pressure. These findings are of considerable interest and suggest that the effect of infusion of propranolol is to block the circulating catecholamines at the sinus node, resulting in a slowing of the sinus rate. The changes in both the recipient and donor atria were comparable; if slowing of the innervated recipient atrium was out of proportion to that of the denervated donor atrium, the effect of lysis of autonomic tone at the sinus node would necessarily be invoked as the cause for the slowing. However, the slowing at the sinus node was comparable in both atria, thus suggesting that blockade of circulating catecholamines was the predominant effect of the infusion of propranolol. The effect of propranolol at the A-V node with an increase in the A-H interval can also be explained by the blockade of circulating catecholamines and a resultant increase in A-V nodal refractoriness.

Only trivial increases in the rate of the donor atrium were produced by norepinephrine and isoproterenol after the administration of propranolol. Competitive inhibition at the beta receptor site in the sinus node best explains these findings.[5] In Patient 5, reflex slowing of the recipient atrium was again seen although this response was somewhat attenuated. Systolic blood pressure increased in Patients 3 and 5 when they were receiving norepinephrine. This was due to stimulation of alpha receptors, which should not be altered by the infusion of propranolol. The A-H interval was not changed by the reinfusion of norepinephrine or isoproterenol after propranolol whereas this interval had previously been shortened by both agents, thus demonstrating that beta blockade was complete at the A-V node.

The intrinsic rate of the recipient atrium in Patient 3 at the initiation of this study was 143 beats/min. None of the drugs administered altered this rate. We suggest that the atrium of this patient had an ectopic tachycardia that was protected from pharmacologic intervention. We have noted in other patients not included in this series that either the donor or recipient atrium can have an ectopic rhythm in isolation, and that typically the rhythm is not controlled pharmacologically.

Clinical implications: Several conclusions can be drawn from these studies. First, the specialized conduction tissue of the heart can be influenced by stimulation and blockade of the autonomic nervous system in the denervated heart. Second, by all pharmacologic means available we have not been able to demonstrate evidence for reinnervation of the transplanted denervated heart. Third, the adrenergic receptor is intact in the denervated heart although evidence suggests that adrenergic nerve fibers are no longer present. This observation supports the original claims of Ahlquist.[16] Fourth, the problem of hypersensitivity in the denervated human heart cannot be determined from these studies, but the concept needs further investigation.

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Chronic Right Bundle Branch Block and Left Posterior Hemiblock

Clinical, Electrophysiologic and Prognostic Observations

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Twenty-one patients with long-term right bundle branch block and left posterior hemiblock were studied electrophysiologically and then followed up prospectively. The group consisted of 19 men and 2 women aged 61 ± 2.7 years (mean ± standard error of the mean). The majority of patients had either hypertensive cardiovascular disease (48 percent) or primary conduction disease (33 percent). Initial electrophysiologic studies revealed A-H intervals of 58 to 152 msec (mean 98 ± 7.7) and H-V intervals of 40 to 80 msec (mean 52 ± 2.1). Six patients (29 percent) had prolonged H-V intervals. The follow-up period ranged from 91 to 1,231 days (mean 671 ± 68). Three of 21 patients (14 percent) needed a permanent pacemaker after development of the following symptomatic conduction disease: sinoatrial block on day 3 of follow-up; second degree atrioventricular (A-V) block, site undetermined, on day 118; and second degree A-V block proximal to the His bundle on day 398. One patient died suddenly (on day 571), and two others died of noncardiac causes.

In conclusion, combined right bundle branch block and left posterior hemiblock was associated with less trifascicular disease than reported previously. The clinical course of most of the patients was benign and the incidence of sudden death was relatively small. Symptomatic conduction disease occurred but could be definitely related to trifascicular disease in only one patient. These short-term data suggest that prophylactic pacemaker insertion is not routinely indicated in patients with chronic right bundle branch block and left posterior hemiblock.

Rosenbaum et al.[1] have suggested that patients with intact atrioventricular (A-V) conduction and chronic right bundle branch block with left posterior hemiblock are at high risk of progression of conduction disease. They have reported a 62 percent incidence rate of heart block over an unspecified follow-up period in patients with right bundle branch block and left posterior hemiblock. Other retrospective studies[2–8] in a limited number of patients support the high risk that heart block will develop in the presence of right bundle branch block and left posterior hemiblock. However, many of the latter studies concern patients whose conduction defects were secondary to acute myocardial infarction.

This study, based on a prospective examination of the clinical findings in patients with chronic right bundle branch block and left posterior hemiblock attempts to define further the natural history of this combination of conduction defects. In addition, observations are presented concerning clinical, electrocardiographic and electrophysiologic findings in this group of patients.

Material and Methods

Patient selection: The study group consisted of 21 patients with combined chronic right bundle branch block and left posterior hemiblock. The

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TABLE I

Clinical Features of 21 Patients with Right Bundle Branch Block and Left Posterior Hemiblock

Case no.	Age (yr) & Sex	Diagnosis	NYHA Class (NYHA)	CHF	Electrocardiogram P-R Interval (sec)	QRS Duration (sec)	QRS Axis (°)
1	73 M	PCD	I	–	0.16	0.14	+100
2	63 M	PCD	I	–	0.18	0.16	+100
3	75 M	PCD	I	–	0.18	0.14	+100
4	42 F	PCD	I	–	0.17	0.12	+120
5	67 M	PCD	I	–	0.16	0.14	+120
6	27 M	PCD	I	–	0.24	0.12	+95
7	66 M	PCD	I	–	0.18	0.12	+150
8	54 M	HCVD	II	+	0.26	0.16	+145
9	61 M	HCVD	II	+	0.20	0.14	+90
10	51 M	HCVD	II	+	0.20	0.16	+150
11	72 F	HCVD	II	+	0.14	0.12	+100
12	66 M	HCVD	II	+	0.22	0.20	+135
13	47 M	HCVD	I	–	0.12	0.12	+130
14	83 M	HCVD	I	–	0.22	0.16	+90
15	70 M	HCVD	I	–	–	0.12	+120
16	57 M	HCVD	I	–	0.12	0.12	+110
17	64 M	HCVD	I	–	0.16	0.12	+110
18	64 M	ASHD	II	–	0.16	0.15	+180
19	63 M	ASHD	II	+	0.22	0.15	+100
20	50 M	ASHD	I	–	0.18	0.13	+110
21	67 M	PMD	IV	+	0.22	0.19	+120
Mean	61	...	...	...	0.18	0.14	+118
SEM	2.7	...	...	...	0.008	0.005	5.1

– = absent; + = present; ASHD = arteriosclerotic heart disease; CHF = congestive heart failure; HCVD = hypertensive cardiovascular disease; NYHA Class = New York Heart Association functional classification; PCD = primary conduction disease; PMC = primary myocardial disease; SEM = standard error of the mean.

criteria utilized for the electrocardiographic diagnosis of these defects were identical to those used in previous series.[2–4,9–13] They included: (1) QRS duration of 0.12 second or greater; (2) an rSR or qR configuration of the QRS complex in lead V_1; and (3) a mean frontal QRS axis between +90° and +180° with the presence of a deep S wave in lead I and a small q wave with a tall R wave in lead III (initial 20 msec vector directed upward and 40 to 60 msec vectors oriented downward).

The study group was part of a large group of patients with various types of intraventricular conduction disease followed up in the Chicago West Side Medical Center (Cook County Hospital, The West Side Veterans Administration Hospital and the University of Illinois Hospital).[14–16] During the 5 years from January 1970 to February 1975, all electrocardiograms in these three hospitals were continuously screened by members of the respective cardiology departments, in order to detect the presence of conduction disease. This report details our experience with patients with chronic right bundle branch block and left posterior hemiblock detected in both the inpatient and outpatient departments.

Criteria for inclusion in the study were: (1) Presence of chronic right bundle branch block and left posterior hemiblock with intact A-V conduction. (2) Absence of clinical cause of right ventricular hypertrophy, which could simulate right bundle branch block and left posterior hemiblock[1] (specifically excluded were patients with mitral stenosis, chronic obstructive pulmonary disease and congenital heart disease). (3) Signing of informed consent form for electrophysiologic study. (4) Agreement to participate in prospective follow-up studies in a conduction disease clinic. Patients with a history of second or third degree A-V block before or at the time of initial study and patients with right bundle branch block and left posterior hemiblock complicating acute myocardial infarction were excluded from the study.

Initial evaluation: All patients were hospitalized upon entering the study. A complete history and physical examination, serial electrocardiograms, chest X-ray films and routine laboratory tests were obtained. On the basis of these data a clinical diagnosis was established for each patient. Diagnostic categories included arteriosclerotic heart disease (typical anginal chest pain or evidence of an old myocardial infarction, or both), hypertensive cardiovascular disease (persistent diastolic pressure greater than 100 mm Hg), primary myocardial disease (cardiomegaly without apparent cardiac cause) and primary conduction disease (right bundle branch block and left posterior hemiblock with normal heart size and without evidence of organic heart disease).

His bundle electrograms were recorded in every patient utilizing previously described catheter techniques.[17,18] Atrial pacing at increasing heart rates was utilized to validate His bundle potentials and to demonstrate latent conduction defects.[19] The following intervals were measured in milliseconds:[18] A-H, a measure of A-V nodal conduction time (mean ± 2 standard deviations; normal 92 ± 38 msec) and H-V, a measure of conduction time in the His-Purkinje system (normal 43 ± 12 msec). Intervals were measured at a paper speed of 200 mm/sec and reflect the mean of 10 consecutive beats. Sinus nodal recovery time was measured upon the sudden cessation of atrial pacing at a rate of 130/min (normal 1,680 msec or less).[18] Refractory periods of the atrium, A-V node and His-Purkinje system were measured with the atrial extrastimulus technique.[20]

Patient follow-up: After initial evaluation, all patients were prospectively followed up in a conduction disease clinic at intervals of 1 to 2 months. Each clinic visit included a history, physical examination and 12 lead electrocardiogram. Electrocardiographic monitoring, by portable tape recorder or prolonged inpatient records, or both, was utilized when transient bradyarrhythmias were suspected. A permanent pacemaker was implanted only in symptomatic patients with documented bradyarrhythmias.

No patient was lost to follow-up study during the study period. If a patient died outside the hospital, details of the death as well as copies of death certificates were obtained. Deaths occurring instantaneously or within 3 hours of the onset of acute symptoms were classified as "sudden." [16]

All information obtained during the initial hospitalization and subsequent clinic visits was recorded by keypunch and stored on IRS database system discs. Specially designed programs were used for data recall and statistical analysis.[16]

Results

Clinical data (Table I): There were 19 men and 2 women aged 27 to 83 years (mean ± standard error of the mean 61 ± 2.7 years). Ten patients (48 percent) had hypertensive cardiovascular disease, three (14 percent) had arteriosclerotic heart disease, seven (33 percent) had primary conduction disease and one (5 percent) had primary myocardial disease. Congestive heart failure was present in seven patients (33 percent) and cardiomegaly by chest roentgenogram in nine patients (43 percent). Thirteen of 21 patients (62 percent) were in cardiac functional class I (New York Heart Association criteria), seven (33 percent) were in class II and one (5 percent) in class IV.

TABLE II

Electrophysiologic Findings (msec) and Follow-Up Data in 21 Patients

Case no.	Intervals						Follow-Up	
	A-H (92 ± 38)*	H-V (43 ± 12)*	Atrial ERP (242 ± 98)*	AVN ERP (300 ± 94)*	VSCS ERP	SRT (988 ± 692)*	Days	Outcome
1	58	64	225	. . .	. . .	1600	1095	. . .
2	82	66	. . .	. . .	. . .	940	817	. . .
3	77	42†	330	. . .	530	1393	91	Died of esophageal carcinoma on day 91
4	93	43	. . .	. . .	. . .	890	513	. . .
5	102	52	280	330	450	770	552	. . .
6	152	43	180	370	. . .	1070	321	. . .
7	92	54	380	390	450	920	268	. . .
8	114	80	290	. . .	. . .	2100	1231	S-A block developed on day 3
9	120	50	. . .	. . .	. . .	700	571	Died suddenly on day 571
10	105	40	. . .	. . .	. . .	830	748	. . .
11	103	47	230	470	. . .	1025	447	. . .
12	130	52	240	270	. . .	850	378	. . .
13	65	50	310	. . .	. . .	800	1149	. . .
14	152	52	. . .	. . .	. . .	540	668	Died of CVA on day 668
15	. . .	58	. . .	. . .	. . .	. . .	678	. . .
16	72	41	210	. . .	. . .	917	564	. . .
17	70	57	300	330	. . .	1000	414	. . .
18	92	57	. . .	. . .	. . .	1100	918	. . .
19	130	48	. . .	555	. . .	1135	712	2° A-V block proximal to H developed on day 398
20	125	42	. . .	. . .	. . .	850	750	2° A-V block developed at unknown site on day 118
21	135	45	320	. . .	. . .	4500	1209	. . .
no. of cases	20	21	12	7	3	20	21	. . .
Mean	98	52	274	388	477	1197	671	. . .
SEM	7.7	2.1	16.7	36.1	26.6	190	68	. . .

*Normal mean ± 2 standard deviations.
†Second degree atrioventricular block developed distal to the His bundle at a paced rate of 150/min.
A-V = atrioventricular; AVN = atrioventricular node; CVA = cerebrovascular accident; ERP = effective refractory period; H = His bundle; S-A = sinoatrial; SEM = standard error of the mean; SRT = sinus nodal recovery time; VSCS = ventricular specialized conduction system.

Electrocardiographic findings (Table I): Twenty of the 21 patients had sinus rhythm at the time of study, and 1 had atrial fibrillation. P-R intervals ranged from 0.12 to 0.26 second (mean ± standard error of the mean 0.18 ± 0.008 second); they were prolonged (greater than 0.20 second) in 6 of the 21 patients. The QRS duration ranged from 0.12 to 0.20 second (mean 0.14 ± 0.005). The frontal QRS axis ranged from +90° to +180° (mean 118 ± 5.1).

Electrophysiologic data (Table II): The A-H interval ranged from 58 to 152 msec with a mean ± standard error of the mean of 98 ± 7.7 msec in 20 patients; the interval was prolonged in 3 (15 percent) of the 20 patients. The H-V interval ranged from 40 to 80 msec (mean 52 ± 2.1) and was prolonged in 6 (29 percent) of the 21 patients. Sinus nodal recovery time, determined in 20 patients, ranged from 540 to 4500 msec (mean 1,197 ± 190) and prolonged in 2 (10 percent).

The atrial effective refractory period, measured in 12 patients, ranged from 180 to 380 msec (mean 274 ± 16.7) and was prolonged (greater than 340 msec) in 1. The A-V nodal effective refractory period, measured in seven patients, ranged from 270 to 555 msec (mean 388 ± 36.1) and was prolonged (greater than 400 msec) in two. The effective refractory period of the ventricular specialized conduction system was determined in three patients and ranged from 450 to 530 msec (mean 477 ± 26.6).

Follow-up data: The follow-up period ranged from 91 to 1,231 days (mean 671 ± 68 days). Progression of conduction disease was documented in 2 (10 percent) of 21 patients. In one (Case 20), types I and II second degree A-V block were demonstrated with tape recorder monitoring on the 118th day of follow-up during hospitalization for recurrent syncope. Initial electrophysiologic studies in this patient had revealed normal conduction intervals and pacing responses. Because His bundle studies were not performed during the episode of second degree A-V block, the site of block in this patient was not known. In the second patient (Case 19), second degree block proximal to His bundle occurred on the 398th day of follow-up during hospitalization for congestive heart failure. Initial electrophysiologic studies in this patient also were within normal limits.

Symptomatic bradyarrhythmia due to sinus nodal dysfunction was noted in another patient (Case 8) or

the 3rd day of follow-up. This patient had a syncopal episode 1 week before admission. Tape recorder monitoring revealed intermittent sinoatrial exit block. Initial electrophysiologic studies revealed a normal A-H (114 msec) and prolonged H-V (80 msec) interval. The patient also had a prolonged sinus nodal recovery time of 2,100 msec. No patient in the series manifested complete heart block.

Permanent pacemakers were implanted in only the three patients described (Cases 8, 19 and 20) with symptomatic bradyarrhythmia. All have remained asymptomatic since pacemaker insertion.

Three patients died. In two, the death was not sudden; one (Case 3) dying of esophageal carcinoma (day 91) and the other (Case 14) of a cerebrovascular accident (day 668). The third patient (Case 9) died suddenly (day 571), and autopsy revealed acute anteroseptal myocardial infarction with total occlusion of the left anterior descending artery.

Comparison of groups: *Patients with primary conduction disease* were compared with those with organic heart disease. There were no significant differences between the two groups in regard to age, sex or electrocardiographic or electrophysiologic variables. All patients with primary conduction disease were in functional class I without evidence of congestive heart failure. The three patients requiring permanent pacemaker insertion (including the two in whom second degree A-V block developed) had organic heart disease. The clinical diagnosis in the latter two patients was arteriosclerotic heart disease.

Patients with a prolonged H-V interval were compared with those with a normal H-V interval. There were no significant differences in clinical features, electrocardiographic findings or electrophysiologic data. Both patients who experienced second degree A-V block had a normal H-V interval. The patient manifesting sinoatrial block had a prolonged H-V interval.

Discussion

Left posterior hemiblock and bifascicular block: Isolated left posterior fascicular block (left posterior hemiblock) is a rare electrocardiographic finding, an observation that reflects several intrinsic protective factors relating to the posterior division.[1] These include (1) A dual blood supply, providing partial protection from ischemic heart disease. (2) A relatively favorable anatomic location, protecting the posterior division from the stress of the left ventricular ejection. (3) The fact that the left posterior division is the broadest of the three fascicles of the trifascicular conduction system making left posterior hemiblock less likely with focal conduction lesions. According to Rosenbaum et al.,[1] left posterior fascicular block usually accompanies right bundle branch block. Simultaneous involvement of the right bundle branch and the posterior division of the left bundle branch implies the presence of extensive conduction disease, with probable involvement of the remaining functioning fascicle (the anterior division of the left bundle branch). Thus, right bundle branch block with left posterior hemiblock is considered a malignant form of bifascicular block.

Prolongation of H-V interval: Recording of His bundle electrograms in patients with right bundle branch block and left posterior hemiblock provides a means of assessing the conduction properties of the remaining functioning fascicle. In this setting the H-V interval is a measure of conduction time in the distal His bundle and the anterior fascicle of the left bundle branch system.[19] Prolongation of the H-V interval in patients with right bundle branch block and left posterior hemiblock probably represents additional slowing in the anterior fascicle and, hence, trifascicular disease.[21] Haft et al.[22] described four such patients and demonstrated H-V prolongation in two. Narula and Samet[11] recorded His bundle electrograms in 15 patients with right bundle branch block and left posterior hemiblock and reported H-V prolongation (greater than 55 msec) in 80 percent, and Levites et al.[23] reported H-V prolongation in 7 (64 percent) of 11 such patients. The 29 percent incidence rate of H-V prolongation in our series is therefore low. The reason for this discrepancy is not apparent. The incidence rate of associated A-V nodal disease in our series, as suggested by A-H prolongation, was also low (15 percent).

H-V prolongation in patients with bifascicular block may carry a high risk of subsequent heart block and is considered by some to be an indication for prophylactic pacemaker insertion.[8,24] We found no evidence to support this view. None of our patients with H-V prolongation later manifested higher grades of A-V block. All are alive and have had a relatively normal clinical course. Permanent pacemaker insertion was indicated in only one of them because of associated sinus nodal dysfunction. Our observations are in agreement with a recent report[16] of patients with right bundle branch block and left anterior hemiblock who were found to have a similar risk of progression of conduction disease whether the H-V interval was prolonged or normal.

Clinical features: The clinical profile of our patients with right bundle branch block and left posterior hemiblock revealed several interesting features. Ninety percent of our patients were male, a finding consistent with previous observations of Rosenbaum et al.[1] and Varriale et al.,[13] who reported, respectively, an 86 percent and 75 percent male preponderance in patients with right bundle branch block and left posterior hemiblock. The most common identifiable cause in our series was hypertensive cardiovascular disease, which was present in about 50 percent of cases (10 of 21 patients). Next in frequency was primary conduction disease (bifascicular block without other evidence of organic heart disease), which was found in 33 percent of our patients. Most of these latter patients were elderly and presumably had idiopathic sclerodegenerative lesions of the bundle branch system secondary to sclerosis of the left cardiac skeleton (Lev's disease).[25] In other series, arteriosclerotic heart disease was the most common etiologic

factor in patients with chronic right bundle branch block and left posterior hemiblock. Ten (44 percent) of 24 patients described by Scanlon et al.,[10] 5 (42 percent) of 12 patients cited by Varriale and Kennedy[13] and 8 (27 percent) of 29 patients reported on by Rosenbaum et al.[1] were considered to have arteriosclerotic heart disease although the criteria for the diagnosis of arteriosclerotic heart disease were not presented. In our series, arteriosclerotic heart disease was an infrequent diagnosis, found in only 14 percent of our patients.

Natural history: progression to advanced heart block: Progression of chronic right bundle branch block and left posterior hemiblock to advanced or complete heart block has previously been demonstrated.[1–3,8,10,13] Rosenbaum et al.[1] reported that in 18 of 29 such patients (62 percent), detected over a 10 year period, advanced or complete heart block developed. The mean follow-up period in their group was not specified, and an unspecified number of their patients had A-V block initially. Kulbertus and Collignon[2] reported on five patients with right bundle branch block and left posterior hemiblock whose condition progressed to complete heart block over an 11 month period, and Castellanos et al.[3] reported on four patients whose defects progressed to advanced heart block over a period of 7 months. They suggested that right bundle branch block with left posterior hemiblock was a precursor of complete heart block, implying that this combination of defects was an indication for prophylactic permanent pacemaker insertion.

There are two reports suggesting that right bundle branch block with left posterior hemiblock is less malignant than suggested by the studies cited. Scanlon et al.[10] described 24 patients followed up for a mean of 25 months; progression to higher grades of A-V block occurred in 5 patients (21 percent) and 1 patient died suddenly. Varriale and Kennedy[13] reported on 12 patients followed up for a mean period of 2.7 years; none experienced advanced heart block or died suddenly. These previously reported studies were retrospective, and details regarding patient selection were not specified in most of them.[1,10,13] In some studies, patients were selected only after the development of advanced or complete heart block.[2,3]

Our series is the first reported prospective study on the natural history of patients with right bundle branch block and left posterior hemiblock. Documented progression of conduction disease was uncommon, occurring in only 10 percent of patients during a mean follow-up period of approximately 2 years. Surprisingly, in one of our two patients with second degree A-V block, the site of block was proximal to the His bundle (A-V nodal) and not trifascicular. The reasons for the relatively low rate of progression of our series is not apparent. There are several possible explanations: (1) The true incidence of progression has been overestimated by some previous workers.[1–3] In keeping with this are conflicting reports regarding frequency of progression of conduction disease: Varriale and Kennedy[13] (0 percent), Scanlon et al.[10] (21 percent) and Rosenbaum et al.[1] (62 percent). We tend to favor this explanation. (2) The previously reported series of Rosenbaum et al. had a high proportion of patients (35 percent) suffering from myocarditis due to Chagas' disease. This disease produces widespread involvement of the conduction system, and prognosis of bifascicular block may be particularly unfavorable.[26] In our series, there was a high incidence rate of hypertensive cardiovascular disease and primary conduction disease, which may be clinically benign. The diagnosis in both of our patients with progression to second degree A-V block was arteriosclerotic heart disease. The prognosis of bifascicular block may reflect the clinical circumstances in which the conduction disease occurred.[16] (3) The incidence of progression in our series may be slightly underestimated. We considered progression only when advanced A-V block was documented electrocardiographically. It is possible that asymptomatic periods of intermittent heart block that escaped documentation could have occurred in our patients. However, the prospective nature of our study should have maximized the diagnostic yield of patients with progression of disease. (4) The follow-up period in our study is relatively short. It is likely that additional patients will manifest progression of conduction disease in the future.

The clinical course of our patients with right bundle branch block and left posterior hemiblock was surprisingly benign. Congestive heart failure was present in a third of the patients, and more than 90 percent were in cardiac functional class I or II. The incidence rate of syncope was 15 percent (3 of 21 patients)[15] as compared to the 50 percent rate reported by Rosenbaum et al.,[1] and sudden death occurred in only one patient. Symptomatic conduction disease occurred, but could be definitely related to trifascicular disease in only one patient.

Clinical implications: The following conclusions are suggested by this study. Right bundle branch block with left posterior hemiblock is associated with less trifascicular disease than reported previously. In patients with intact A-V conduction the clinical course is relatively benign with a small incidence of Adams-Stokes attacks and sudden death. Progression to advanced or complete A-V block is uncommon and limited to those with diagnosed organic heart disease. Our short-term data suggest that prophylactic demand pacemaker insertion is not routinely indicated in asymptomatic patients with chronic right bundle branch block and left posterior hemiblock with intact A-V conduction although a longer follow-up period is indicated. These conclusions do not apply to patients with similar conduction defects complicating acute myocardial infarction.

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First Derivative of the Apex Cardiogram and Systolic Time Intervals in Evaluation of Myocardial Contractility in Man

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The sensitivity of various systolic time intervals and measurements derived from the first derivative (dp/dt) of the calibrated apex cardiogram were investigated to assess the value of this noninvasive method for detecting changes in myocardial contractility in man. The electrocardiogram, carotid arterial pulse tracing, phonocardiogram and calibrated apex cardiogram were simultaneously recorded on frequency modulated magnetic tape in 15 normal subjects before and after administration of angiotensin, isoproterenol and propranolol. All measurements, including the ratio (dp/dt)/P, a new variable derived from the apex cardiogram, were obtained by computer wave recognition and measurement programs.

Significant changes occurred mainly in the early phases of the cardiac contraction cycle. Whereas systolic time intervals provided indirect information in regard to the rate of rise of intraventricular pressure, more direct information on changes in myocardial contractility was obtained from the rate of rise of the apex cardiogram. Mean control values for (dp/dt)/P derived from the calibrated apex cardiogram ranged between 29 and 35. These values are comparable with reported (dp/dt)/P ratios derived from left ventricular pressure data. A significant increase in (dp/dt)/P of the apex cardiogram was provoked by isoproterenol. The results of our study suggest that (dp/dt)/P of the calibrated apex cardiogram may be useful as a new noninvasive index of myocardial contractility.

Noninvasive techniques for cardiac evaluation have received much attention in recent years. Measurement of systolic time intervals, such as preejection period (PEP), left ventricular ejection time (LVET) and the ratio PEP/LVET has been emphasized by Weissler and associates.[1,2] Other subdivisions of systole have successfully been used for indirect evaluation of cardiac contractility.[3–5] However, most of these intervals are influenced by many variables, such as ventricular volume and preload, peripheral resistance as well as the level of neurohumoral cardiostimulatory activity. Only with accurate control of these variables can the response in systolic time intervals be employed as a quantitative measure of myocardial contractility.[5]

Recently, more direct methods have been introduced for detecting changes in the myocardial contractile state in intact man. Measurement of the time from the onset of ventricular contraction to the peak of the first derivative (dp/dt) of the apex cardiogram has been advocated by Reale.[6] Since the introduction of calibrated apex cardiography, other indexes related to the magnitude of dp/dt of the apex cardiogram have been proposed.[7]

The purpose of this study was to compare the sensitivity of different systolic time intervals and measurements derived from dp/dt of the apex cardiogram in the noninvasive assessment of left ventricular performance in man. Specifically, we determined the effect of vasoac-

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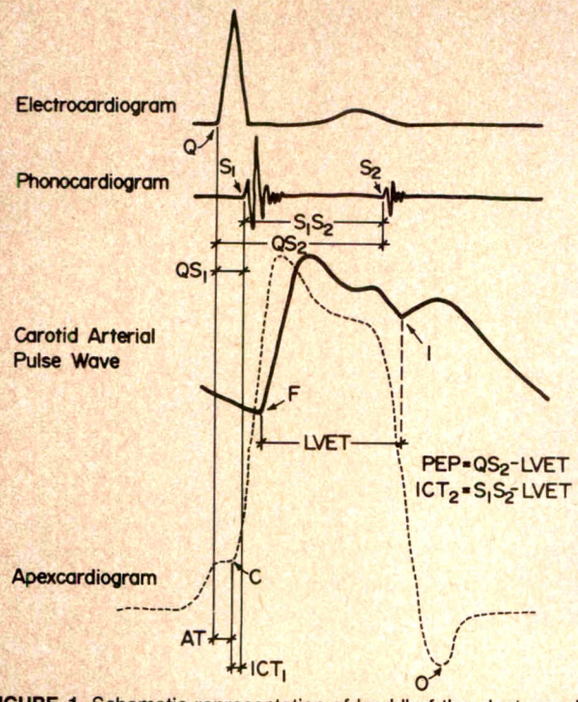

FIGURE 1. Schematic representation of lead II of the electrocardiogram, the phonocardiogram, carotid arterial pulse wave and apex cardiogram. F and I = upstroke and incisura of the carotid arterial pulse wave; C and O = beginning and nadir, respectively, of the apex cardiogram; Q = onset of QRS complex; S_1 and S_2 = onset of the first and second heart sounds.

tive drugs on the ratio (dp/dt)/P derived from the apex cardiogram, a recently introduced measurement.[8–11] This ratio was computed in a manner analogous to that of the ratio (dp/dt)/P derived from left ventricular pressure data. The latter is used to determine maximal no-load velocity of shortening of myocardial elements since it is said to be essentially independent of preload and afterload.[12,13] The measurement of the various indexes was performed by computer pattern recognition and measurement programs with clearly defined criteria.

Methods

Material and Procedures

Fifteen subjects, 14 male and 1 female, all without cardiovascular disease were studied. Their ages ranged from 19 to 47 years. The electrocardiogram (lead II), phonocardiogram, carotid arterial pulse tracing and apex cardiogram were recorded simultaneously on magnetic tape before, during and after infusion of vasoactive drugs. Angiotensin was used to increase total peripheral resistance, and isoproterenol and propranolol were used to alter myocardial contractility. The first two drugs were administered to 10 subjects by slow intravenous infusion after dilution in normal saline solution. Infusion rates ranged from 0.5 to 3 μg/min. Infusion was regulated to obtain a significant change in indirect arterial pressure as determined by frequent monitoring. Propranolol was injected intravenously 25 minutes after the end of the isoproterenol infusion, in a total dose of 5 mg in 10 subjects and 10 mg in an additional group of 5 subjects. Control recordings were obtained before each intervention. Sufficient time (15 to 20 minutes) for a return to the normal state was allowed between periods of drug administration. Angiotensin was always given first, followed by isoproterenol and propranolol.

Recording Equipment

Heart sounds were recorded with a Hewlett-Packard dynamic microphone and amplifier using a high-pass filter with nominal frequency cut-off of 100 hertz. The microphone was placed over the upper part of the precordium in a position optimal for recording the initial high frequency vibrations of the first and second heart sounds.

The transducers and methods used for recording the carotid arterial pulse tracing[14] and apex cardiogram[7,15] have previously been described. Both systems have an infinite time constant and delay time of less than 1.5 msec. The apex beat was recorded with the patient in the left recumbent position and in expiratory apnea. The curves were monitored on a four channel oscilloscope. Apical impulse recordings were calibrated in units of pressure variation (mm Hg) as previously reported.[7,15] These recordings graphically depict the pressure or force exerted by the heart on the thoracic wall during contraction. Conversion of the analog data to digital form was carried out with a sampling rate of 250 points/sec.

Measurements and Calculations

Various systolic time intervals were obtained using automatic wave recognition and measurement programs, details of which have been published.[16] The computer programs have been implemented to locate the C and O points of the apex cardiogram and the onset of the first heart sound.

The magnitude of the first derivative of the calibrated apex cardiogram expressed in millimeters of mercury per second, and the time from the onset of the systolic rise (C point) of the apex cardiogram to the location of peak dp/dt were calculated from the values on digital tape. The ratio (dp/dt)/P of the apex cardiogram was computed every fourth msec over an interval of 112 msec starting 12 msec after point C of the apex cardiogram. Only the maximal (dp/dt)/P ratios obtained during this interval in the control records and those obtained during drug administration were compared. The protodiastolic nadir (O point) of the calibrated tracing was used as reference level for the determination of pressure. Total height of the apex cardiogram was measured as the vertical distance between point O and the highest point of the systolic deflection of the apex cardiogram.

Calibrated apex cardiograms do not differ in configuration from the uncalibrated standard displacement apex cardiogram when these tracings are recorded with devices that have an adequate time constant. When digital procedures are used to compute the first derivative, one can also derive (dp/dt)/P ratios from uncalibrated recordings. Because changes in recording gain with such techniques alter dp/dt to an extent similar to the height of the curve, the quotient (dp/dt)/P remains unaffected.

The following intervals of the cardiac cycle were automatically calculated (Fig. 1):

1. Total electromechanical systolic interval (Q-S_2), measured from onset of the QRS complex to the first high amplitude, high frequency vibrations of the aortic component of the second heart sound.

2. Left ventricular ejection time (LVET), measured from beginning of the upstroke to the incisura of the carotid arterial pulse tracing.

3. Preejection period (PEP), derived by subtracting left ventricular ejection time from the Q-S_2 interval.

TABLE I

Systolic Time Interval Measurements (msec) and Ratios Without Correction for Heart Rate*

	Study 1 (no. = 10)		Study 2 (no. = 8)		Study 3 (no. = 15)	
Measurement	Control	Angiotensin	Control	Isoproterenol	Control	Propranolol
$Q\text{-}S_2$	376 ± 47	409 ± 49	379 ± 45	319 ± 38	386 ± 39	405 ± 37
LVET	275 ± 38	292 ± 33	277 ± 36	239 ± 39	281 ± 32	287 ± 26
PEP	101 ± 20	116 ± 27	102 ± 21	78 ± 11	105 ± 15	118 ± 21
$S_1\text{-}S_2$	310 ± 45	344 ± 41	313 ± 36	254 ± 38	314 ± 35	338 ± 31
AT	35 ± 12	39 ± 14	33 ± 11	29 ± 7	33 ± 7	37 ± 7
$Q\text{-}S_1$	61 ± 8	62 ± 11	65 ± 10	64 ± 7	67 ± 8	64 ± 12
ICT	64 ± 17	76 ± 21	59 ± 13	46 ± 7	68 ± 11	76 ± 16
ICT_1	32 ± 7	21 ± 6	28 ± 12	32 ± 5	33 ± 5	25 ± 9
ICT_2	39 ± 20	54 ± 23	38 ± 14	17 ± 5	36 ± 9	52 ± 13
C-O	453 ± 64	504 ± 51	451 ± 35	396 ± 43	463 ± 36	484 ± 35
$S_2\text{-}O$	104 ± 28	124 ± 17	96 ± 10	83 ± 22	109 ± 16	115 ± 15
PEP/LVET†	37 ± 8	40 ± 9	37 ± 8	34 ± 8	38 ± 6	41 ± 7
$LVET/ICT_2$	8.7 ± 4.4	6.5 ± 3.1	8.4 ± 4.1	15.3 ± 5.5	8.3 ± 2.6	5.8 ± 1.8
C-O/LVET†	160 ± 10	168 ± 10	155 ± 7	153 ± 8	161 ± 6	165 ± 8

* Values are expressed as means ± standard deviation. Relations between the various time intervals (for example, $ICT = ICT_1 + ICT_2$) are not always preserved in this table because the number of cycles used differed for different time intervals.

† Ratios multiplied by 100.

AT = electromechanical activation time; C-O = interval between C and O points in the apex cardiogram; ICT = isovolumic contraction time; ICT_1 = interval between C point of apex cardiogram and onset of first heart sound; ICT_2 = interval between onset of first and second heart sounds minus left ventricular ejection time; LVET = left ventricular ejection time; PEP = preejection period; $Q\text{-}S_1$ = interval from onset of QRS complex to onset of first heart sound; $Q\text{-}S_2$ = total electromechanical systolic interval; $S_1\text{-}S_2$ = interval between onset of first heart sound and beginning of aortic component of second heart sound; $S_2\text{-}O$ = interval from beginning of second heart sound to O point of apex cardiogram.

TABLE II

Percent Change in Systolic Time Intervals and Ratios and Their Statistical Significance After Correction for the Effects of Heart Rate

	Angiotensin		Isoproterenol		Propranolol	
Measurement	%	*P*	%	*P*	%	*P*
$Q\text{-}S_2$*	+1.8	<0.05	−8.6	<0.0005	+1.5	<0.025
LVET*	−0.3	NS	−5.6	<0.01	−1.9	<0.025
PEP*	+9.5	<0.01	−17.7	<0.005	+9.0	<0.005
$S_1\text{-}S_2$*	+4.4	<0.005	−12.4	<0.0005	+3.5	<0.01
AT*	−8.3	NS	+11.5	NS	+3.1	NS
$Q\text{-}S_1$*	−7.0	NS	+7.2	NS	−7.1	<0.01
ICT	+18.5	<0.05	−22.8	<0.05	+11.4	<0.025
ICT_1	−33.3	<0.025	+15.1	NS	−24.1	<0.025
ICT_2	+39.6	<0.005	−55.3	<0.005	+45.1	<0.0005
C-O*	+6.2	<0.0005	−7.7	<0.01	+2.0	NS
$S_2\text{-}O$*	+15.9	<0.005	−2.6	NS	+2.3	NS
PEP/LVET	+7.2	<0.05	−9.6	<0.05	+9.9	<0.005
$LVET/ICT_2$	−26.2	<0.005	+80.7	<0.005	−29.1	<0.005
C-O/LVET	+5.6	<0.025	−1.2	NS	+2.3	=0.06

* Correction for the effects of heart rate was made for these intervals.

NS = not significant; *P* = probability value; other abbreviations as in Table I.

4. PEP/LVET ratio.

5. Interval from onset of the QRS complex to onset of the first heart sound ($Q\text{-}S_1$) and interval between onset of the first heart sound and beginning of the aortic component of the second heart sound ($S_1\text{-}S_2$).

6. Electromechanical activation time (AT), measured from onset of the QRS complex to onset of the systolic upstroke of the apex cardiogram.

7. Interval between the C point and the O point (C-O) on the apex cardiogram and the ratio of this interval to left ventricular ejection time.

8. Isovolumic contraction time (ICT), derived by subtracting the electromechanical activation time from the preejection period. The isovolumic contraction time was divided into two components: ICT_1, the interval between the C point of the apex cardiogram and the onset of the first heart sound, and ICT_2, derived by subtracting the left ventricular ejection time from $S_1\text{-}S_2$. The ratio $ICT_2/LVET$ was also computed.[4]

9. Time from the beginning of the second heart sound to the O point of the apex cardiogram ($S_2\text{-}O$), which is related to the isovolumic relaxation period.

Heart rate was determined by dividing the average R-R interval into 60. For all measurements representative values were calculated from the beats available in 5 seconds of recording. Three to four sets of recordings were available for each of the three periods of drug administration and the three corresponding control periods. Only the mean values of these sets were used in the final analysis.

To correct for the effects of heart rate all time intervals that were significantly correlated with heart rate were expressed as a percent of the normal predicted values using

our own regression equations and those of Weissler et al.[1] The regression equations relating various intervals (in milliseconds) with heart rate used for correction for heart rate were calculated from the results of the control recordings. The equations for Q-S_2, S_1-S_2, left ventricular ejection time, preejection period and the Q-S_1 interval were very similar to those described by Weissler et al.[1,17]

The statistical significance of the differences between values obtained during the control and corresponding drug intervention periods was calculated using Student's one-tailed paired *t* test.

Results

Angiotensin increased the blood pressure from an average of 121 ± 14 mm Hg systolic and 73 ± 9 diastolic to 148 ± 14 and 101 ± 7 mm Hg, respectively. After isoproterenol, systolic blood pressure increased by an average of 11 mm Hg and diastolic pressure decreased by 6 mm Hg. No significant change in blood pressure occurred after injection of propranolol. Heart rate was slowed by angiotensin from a mean control value of 75 ± 12 beats/min to 66 ± 10; it increased by 20 beats/min after isoproterenol and decreased by 12 beats/min after propranolol.

Influence of vasoactive drugs on systolic time intervals: The effects of angiotensin, isoproterenol and propranolol on various systolic time intervals and on ratios derived from these intervals are given in Tables I and II. Table I lists the results without correction for heart rate, and Table II shows the percent deviations in various intervals after correction for heart rate. The most striking changes occurred in the preejection period and isovolumic contraction phases. The direction of these changes was in agreement with findings by others.[18–20]

The preejection period increased significantly after angiotensin and propranolol and decreased after isoproterenol. A significant decrease occurred after isoproterenol in the Q-S_2 and S_1-S_2 intervals, left ventricular ejection time and the isovolumic contraction phase. The lengthening of Q-S_2 after angiotensin was mainly due to prolongation of the preejection period since left ventricular ejection time was not significantly affected. Angiotensin did prolong the S_2-O interval, which is related to the isovolumic relaxation period. The interval C-O of the apex cardiogram, which includes the isovolumic contraction time, left ventricular ejection time and S_2-O, increased significantly after angiotensin and decreased after isoproterenol. The ratio PEP/LVET demonstrated less alteration than the ratio LVET/ICT_2.

Effects of the vasoactive drugs on the apex cardiogram: There were no significant changes in total systolic deflection of the calibrated apex cardiogram induced by the drugs.

Maximal dp/dt of the apex cardiogram was significantly correlated with heart rate (r = 0.40; no. = 90). The slope of the regression equation obtained in these 15 subjects was 6.4. In other words the magnitude of dp/dt of the calibrated apex cardiogram increased approximately 64 mm Hg/sec when heart rate increased 10 beats/min.

Isoproterenol provoked a significant (P <0.05) increase of 56 percent in magnitude of peak dp/dt of the calibrated apex cardiogram even after correction for the effect of heart rate. The respective average decreases seen after propranolol and angiotensin were 17 (P <0.025) and 7 (not significant) percent of the corresponding control values.

The time from the onset of the systolic rise of the apex cardiogram to peak dp/dt decreased by 23.9 percent, but this change was not significant after correction for the effect of heart rate. The peak time interval remained essentially unchanged after administration of angiotensin and propranolol (Table III).

TABLE III

Means and Standard Deviations of Measurements Derived from the Derivative of the Apex Cardiogram

Measurement	Study 1 (no. = 6)		Study 2 (no. = 5)		Study 3 (no. = 10)	
	Control	Angiotensin	Control	Isoproterenol	Control	Propranolol
Time C-maximal dp/dt (msec)	54 ± 18	49 ± 7	54 ± 9	43 ± 6	53 ± 8	54 ± 11
Maximal dp/dt (mm Hg/sec)	555 ± 246	435 ± 136	626 ± 274	1058 ± 420	601 ± 237	464 ± 158
Time C-maximal (dp/dt)/P	33 ± 7	33 ± 5	34 ± 7	28 ± 11	34 ± 11	33 ± 11
Maximal (dp/dt)/P	29.7 ± 5.2	33.4 ± 6.0	33.7 ± 6.6	57.3 ± 20.2	35.7 ± 4.9	33.6 ± 4.9

TABLE IV

Percent Change in Apex Cardiogram Derivative Measurements and Their Statistical Significance After Correction for the Effects of Heart Rate

Measurement	Angiotensin		Isoproterenol		Propranolol	
	%	*P*	%	*P*	%	*P*
Time C-maximal dp/dt (msec)	−7.9	NS	−23.9	NS	−3.6	NS
Maximal dp/dt (mm Hg/sec)	−7.3	NS	+55.7	=0.05	−16.7	<0.025
Time C-maximal (dp/dt)/P	0.0	NS	−17.1	<0.05	−5.2	NS
Maximal (dp/dt)/P	+12.2	<0.025	+69.7	<0.025	−5.9	=0.06

* Correction for the effects of heart rate was made for the time from C to maximal dp/dt and maximal dp/dt, which were significantly correlated with heart rate.

The magnitude of the actual maximal ratio (dp/dt)/P ranged between 29 and 35 during the control recordings. In any given subject, measurement of maximal ratio (dp/dt)/P from the apex cardiogram was highly reproducible during the different control periods.

Peak (dp/dt)/P ratio derived from total pressure variations of the apex cardiogram increased significantly by almost 70 percent ($P < 0.025$) after isoproterenol but was only slightly affected by propranolol and angiotensin (Table IV). The increase after angiotensin was significant ($P < 0.025$), whereas the decrease after propranolol reached the significant level of $P = 0.06$. After isoproterenol the peak (dp/dt)/P ratio of the apex cardiogram occurred 6 msec earlier than during the control period. The maximal (dp/dt)/P ratio occurred on average 28 to 34 msec after point C of the apex cardiogram and fell always within the isovolumic contraction phase (Table III).

The typical effects of the three drugs are depicted in Figures 2 to 4.

Discussion

The rate of rise of intraventricular pressure has commonly been used to evaluate the contractile state of the heart.[12] In this investigation we used various systolic time intervals and measurements related to rate of rise of the apex cardiogram to assess changes in rate of rise of left ventricular pressure in a noninvasive approach to study cardiac performance.

Systolic Time Intervals

Changes in systolic time intervals induced by vasoactive drugs occurred mainly in the early phases of contraction. The preejection period and isovolumic contraction phase decreased significantly after isoproterenol and increased after administration of angiotensin and propranolol. The shortening or lengthening in time required for intraventricular pressure to reach arterial diastolic pressure levels provide indirect evidence that the rate of rise of left ventricular pressure is being affected by these drugs. It is widely recognized, however, that hemodynamic variables

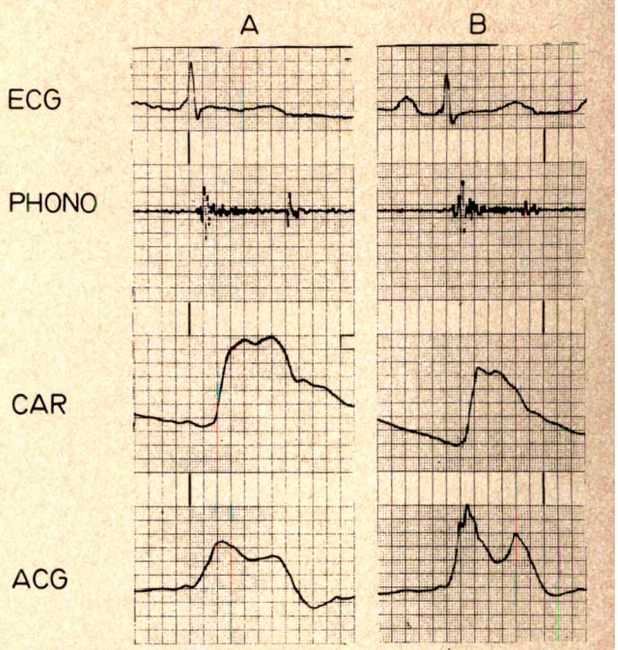

FIGURE 2. Effect of isoproterenol. **A,** control. **B,** after infusion. The systolic rise of the apex cardiogram in **B** is much steeper than in **A** and the systolic plateau presents a retraction, a feature characteristic of high velocity of contraction and decreased left ventricular volume. The dp/dt of the apex cardiogram was not recorded as an analog signal and is therefore not represented on this figure. For explanation see Methods. ACG = apex cardiogram; CAR = carotid arterial pulse tracing; ECG = electrocardiogram; Phono = phonocardiogram.

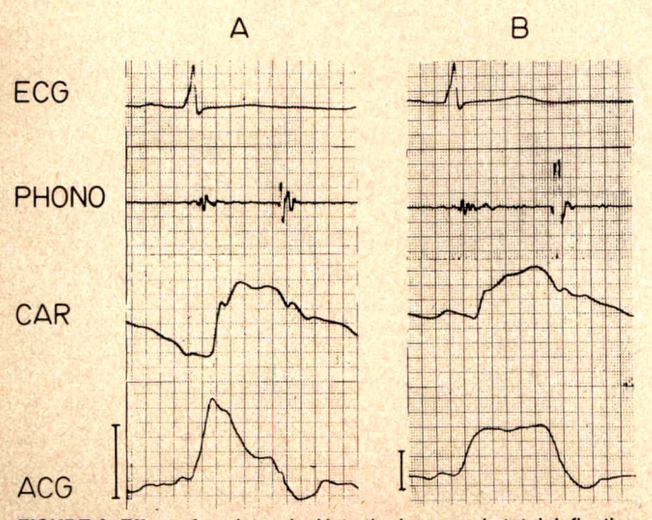

FIGURE 3. Effect of angiotensin. Note the increase in total deflection of the apex cardiogram and the change in systolic configuration in **B,** consisting of obliteration of the E point and a further rise in the systolic plateau. This sustained character of the apical impulse is typical for pressure-loaded situations. The vertical bars correspond to 20 mm Hg. Abbreviations as in Figure 2.

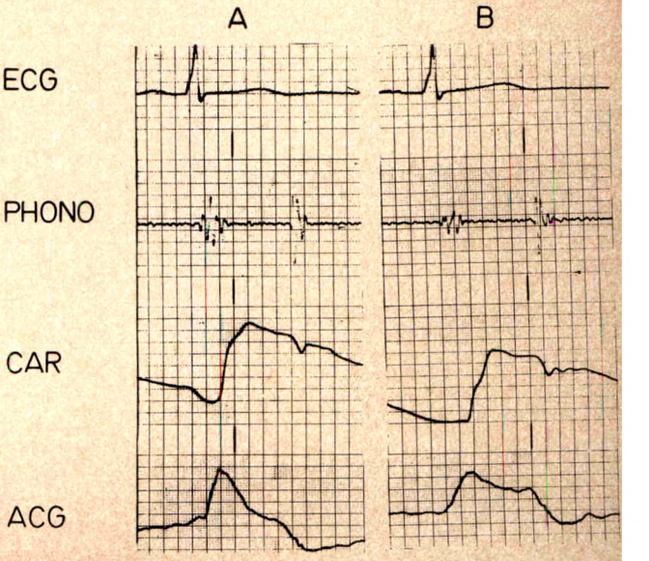

FIGURE 4. Effect of propranolol, 5 mg intravenously. **A,** control. **B,** after intravenous injection. Heart rate decreased by 10 beats/min. No significant changes in configuration are visible. Abbreviations as in Figure 2.

other than myocardial contractility alter the temporal phenomena of the cardiac contraction cycle. The most important factors are heart rate, peripheral resistance and afterload, ventricular end-diastolic filling pressure or preload, stroke volume and the ventricular activation pattern.[1–5,17–21] Only when all these variables are kept constant or taken into consideration do changes in systolic time intervals reflect changes in the rate of rise of intraventricular pressure and myocardial contractility.[5]

No significant differences between control values for electromechanical activation time and results after isoproterenol, propranolol or angiotensin could be demonstrated in our study. Changes in preejection period induced by these drugs are thus mainly due to alterations in isovolumic contraction time. The increase in diastolic blood pressure was mainly responsible for the increase in preejection period and isovolumic contraction time after angiotensin, as well as for the observed increase in the S_2-O interval, which is related to the isovolumic relaxation period.[22] A diminished stroke volume or decreased myocardial contractility should be considered responsible for most of the changes in systolic time intervals induced by propranolol.[18,19] Both a decrease in diastolic pressure and an enhanced rate of rise of intraventricular pressure were elicited by isoproterenol, leading to the decrease in preejection period, isovolumic contraction time and left ventricular ejection period, the small decrease in PEP/LVET ratio and the change in $LVET/ICT_2$ quotient. The effect of adrenergic receptor activation and blockade on systolic time intervals has been studied extensively by Harris et al.[18] and others.[19,20]

Whereas systolic time intervals provide indirect evidence of changes in the rate at which intraventricular pressure rises, more direct information in this respect can be gained from the first derivative of the apex cardiogram.

Apex Cardiographic Measurements

A significant correlation between simultaneously recorded first derivatives of the apex cardiogram and left ventricular pressure has been demonstrated by several authors.[6–11,23]

Peak dp/dt time: The time interval from the onset of ventricular contraction to the peak of the first derivative of the apex cardiogram decreased significantly after isoproterenol in our study, confirming the observations of Reale.[6] But the shortening of this interval, as well as its prolongation after propranolol, was not significant after correction for the effects of heart rate.

Magnitude of the first derivative: Calibration of the apex cardiogram using devices recording precordial movement[24,25] and variations in precordial pressure[7,11,15] made it possible to include the magnitude of the first derivative in the evaluation of the contractile state of the heart. Positive inotropic interventions in dogs provoked a marked increase in peak dp/dt of both the apex cardiogram and left ventricular pressure, whereas negative inotropic interventions, vagal stimulation and propranolol had the opposite effect.[7] The data from our study confirm these observations. The percent change in dp/dt of the apex cardiogram exceeded the percent change of almost all the systolic time intervals, thus indicating that dp/dt of the apex cardiogram is not only more specific, but also more sensitive in detecting changes in rate of rise of left ventricular pressure. However, the usefulness of even left ventricular dp/dt is limited because this index is also influenced by factors extraneous to contractility, such as variations in heart rate, ventricular preload and afterload.[12] We observed a significant correlation between the rate of rise of the apex cardiogram and heart rate. The same was found for left ventricular dp/dt in dogs by other investigators.[26,27] Furthermore, calibrated apex cardiography is still largely dependent on the recording technique. Although standardization can reduce the intraindividual variability, total height of the curves, and hence also of the derivative, may vary according to the respiration phase and the position of the patient.[11]

Ratio (dp/dt)/P from the apex cardiogram: Use of maximal dp/dt as a measure of myocardial contractility has been mostly replaced by the normalized ratio (dp/dt)/P based on left ventricular pressure data.[12,13] It has been shown that the ratio of the rate of rise to the simultaneous ventricular pressure approximates, under certain assumptions, the contractile element velocity during isovolumic systole. The maximal no-load velocity of myocardial contractile elements (Vmax) obtained by extrapolation of pressure velocity data, as well as the actual maximal shortening velocity, was found useful in separating patients with cardiac failure from normal subjects.[12,13,28,29]

The high correlation between first derivatives obtained from apex cardiography and left ventricular pressure curves suggested that a similar ratio (dp/dt)/P based on the apex cardiogram might be of value.[7] A significant correlation could be demonstrated between the ratio dp/dt to instantaneous P from simultaneously recorded apex cardiograms and left ventricular pressure data in dogs subsequently investigated during various hemodynamic interventions.[10,11]

The mean value for (dp/dt)/P based on the apex cardiogram in our study in normal subjects ranged between 29 and 35. In any given subject, measurements of the ratio (dp/dt)/P were highly reproducible during the three different control periods occurring approximately 45 minutes apart.

The consistency of the results based on the rate of rise of the apex cardiogram as well as on various time intervals may partly be due to the automatic wave recognition programs and the computer analysis used in our study. Computer programs depend on clearly defined criteria rather than on subjective impressions in the delineation of the onset of the various waves.[16] The values of (dp/dt)/P of the apex cardiogram re-

ported here are only slightly lower than maximal ratios of left ventricular (dp/dt)/P derived by several investigators[13,29,30] from the isovolumic phase in man.

Clinical Implications

The influence of angiotensin on "myocardial contractility" in the intact heart is not well known. The lengthening of the preejection period and PEP/LVET ratio may indicate a possible decrease in contractility. However, the ratio (dp/dt)/P of the apex cardiogram increased slightly but significantly in our study, pointing to a possible increase in "myocardial contractility." The fact that only barely significant alterations were seen after administration of propranolol may be attributed to the use of rather small doses and to the generally reduced sympathetic tone in the normal resting subject, which leaves little room for the beta adrenergic blocking agent to demonstrate its influence. However, the marked increase in (dp/dt)/P of the apex cardiogram after administration of isoproterenol, consistent with the enhanced myocardial contractile state, suggests that this new measurement may be useful as an indirect noninvasive index of myocardial contractility.

The value of (dp/dt)/P of the apex cardiogram in estimating cardiac function must await further studies in patients with cardiac abnormalities, especially those with heart failure. The few investigations performed thus far in patients with heart disease[9,31] seem to underscore the expectations prompted by experimental studies in dogs.[8,10,11]

It is important to stress that apex cardiograms should be recorded with adequate apparatus.[22,25] When they are recorded with devices that have too short a time constant already partially differentiated curves are obtained. The relations of such curves to their derivative may not be quantitatively comparable with results obtained from tracings recorded with devices having a sufficiently long time constant.

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Mahaim and James Fibers As a Basis for a Unique Variety of Ventricular Preexcitation

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This report concerns pathologic findings in a 54 year old woman with intermittent preexcitation who died of carcinoma of the breast. Electrocardiograms revealed predominantly normal sinus rhythm with a normal P-R interval and narrow QRS complex. Episodes of sinus rhythm, short P-R interval and QRS widening (with delta wave) were also recorded. During preexcitation QS complexes were noted in leads II, III, aVF, V_1 and V_4 to V_6. Delta waves were negative in leads II, III, aVF and V_1, isoelectric in leads V_4 to V_6 and positive only in leads I, aVL, V_2 and V_3. This case thus defies classification into any known variety of preexcitation.

Complete serial sections, cut through the entire conduction system and both atrioventricular (A-V) rims, totaled 18,600 sections. These revealed no bundle of Kent. Instead, Mahaim fibers histologically identified as His bundle tissue gave off from the A-V bundle to both the right and the left sides of the septum associated with the normal fibers of James. This case reveals that (1) fibers of James can bypass the A-V node, (2) fibers of Mahaim can conduct, and (3) there are types of preexcitation in addition to types A and B.

This report concerns a clinically unusual case of intermittent Wolff-Parkinson-White syndrome. The conduction system of the heart and both atrioventricular (A-V) rims were serially sectioned, and the findings showed that the fibers of James[1] and Mahaim[2] probably played a role in the genesis of the preexcitation.

Clinical Review

This 54 year old woman had a right radical mastectomy for carcinoma of the breast in December 1953. She did well for 5 years. However, in the fall of 1958 metastasis developed to the thyroid and lungs. A hemithyroidectomy and pituitary stalk resection were performed. In November 1959 she had a total hypophysectomy. In April 1960 enlarged cervical lymph nodes were noted with evidence of liver disease. The patient was treated with prednisone, and liver function returned to normal.

Between July and September 1960 she had signs of congestive heart failure, arrhythmias and pericardial effusion. Tumor cells were present in the pericardial fluid. Accordingly, in September 1960 she was given a dose of 3,000 rads to the mediastinum. Her subsequent course deteriorated progressively and she died in November 1960.

Analysis of Electrocardiograms

An electrocardiogram on September 9, 1958 (*Fig. 1, left panel*) was within normal limits, with a P-R interval of 0.16 second and a narrow QRS complex.

An electrocardiogram on August 19, 1960 (*Fig. 1, right panel*) revealed a sinus tachycardia with a normal P-R interval, narrow QRS complex, a Q_3-T_3 pattern, and nonspecific S-T and T wave changes, possibly caused by digitalis. Low voltage of the QRS complex had developed in all leads.

Two electrocardiograms taken on November 8, 1960 (*Fig. 2*) revealed atrial fibrillation and atrial flutter (not illustrated) with ventricular response av-

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eraging approximately 100/min. Two types of ventricular complexes were present on both occasions, one a narrow, the other a prolonged QRS complex. Narrow complexes characterized by a frontal QRS axis of approximately +45° resembled those recorded on August 19, 1960. The wide complexes (QRS 0.12 second) were characterized by a QS configuration and upright T waves in leads II, III, aVF, V_1, V_5 and V_6 and by an rS configuration in leads V_2 to V_4. These wide complexes occurred singly and in groups of two and three. When occurring as triplets, they were irregular. Subsequent electrocardiograms obtained during sinus rhythm demonstrated that these wide complexes reflected preexcitation (see later).

An electrocardiogram on November 9, 1960 (*Fig. 3*) revealed conversion to sinus rhythm with ventricular preexcitation. The P-R interval was 0.10 second, and the QRS duration 0.12 second; delta waves were present. The pattern of preexcitation fitted no previously reported classification, in that QS complexes were present in leads II, III, aVF, V_1 and V_4 to V_6. Delta waves were negative in leads II, III, aVF and V_1, isoelectric in leads V_4 to V_6 and positive only in leads I, aVL, V_2 and V_3. Initial depolarization was thus directed leftward and superiorly in the frontal plane and directed toward leads V_2 and V_3 and away from V_1 and V_4 to V_6. It is difficult to visualize the ventricular activation sequence during preexcitation. The limb leads and lead V_1 suggest preexcitation of the posterior right ventricle. The QS configuration in leads V_4 to V_6 suggests preexcitation of the apex or left lateral wall, or both.

An electrocardiogram on November 15, 1960 (*Fig. 4*) revealed sinus rhythm, enlarged P waves, a normal P-R interval of 0.18 second, an axis of −60° and a narrow QRS complex resembling those seen in Figure 1 (right panel). However, the T waves were now inverted in leads I, III, aVL and aVF and from V_3 to V_6, and the S-T segment was depressed in leads II and V_3 to V_6.

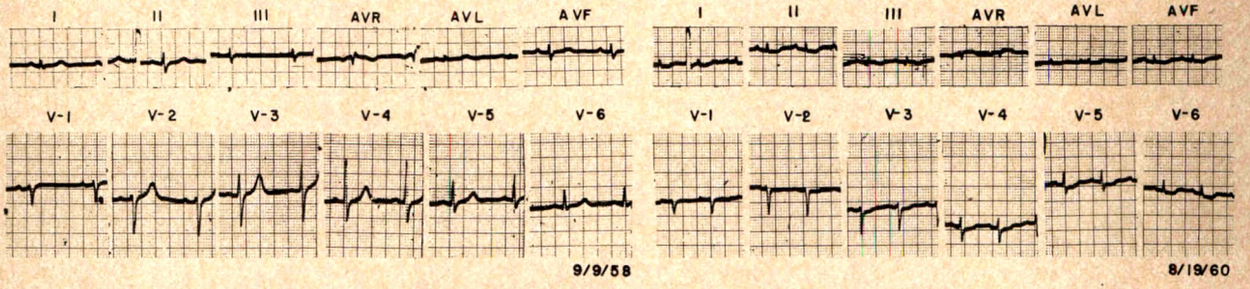

FIGURE 1. Electrocardiograms of September 9, 1958 and August 19, 1960. The P-R interval and QRS duration are normal in both. Low voltage and an abnormal ST-T configuration are evident in the 1960 tracing.

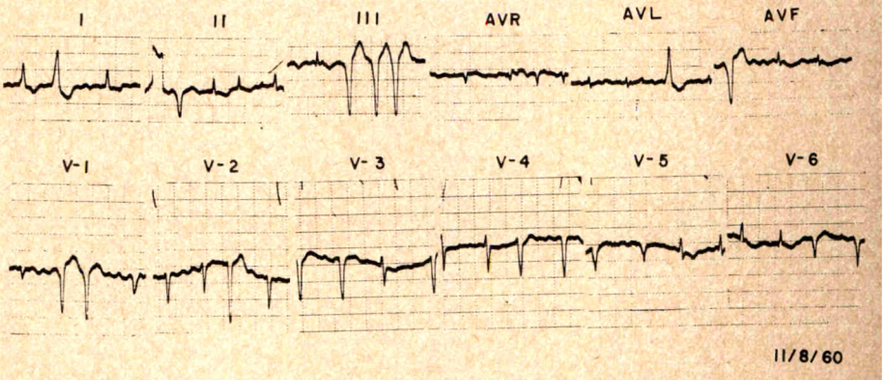

FIGURE 2. Electrocardiogram of November 8, 1960. The tracing reveals atrial fibrillation with intermittent preexcitation, characterized by QRS complexes widened by a delta wave to 0.12 second; the ST-T wave points in direction opposite to that of the QRS complex.

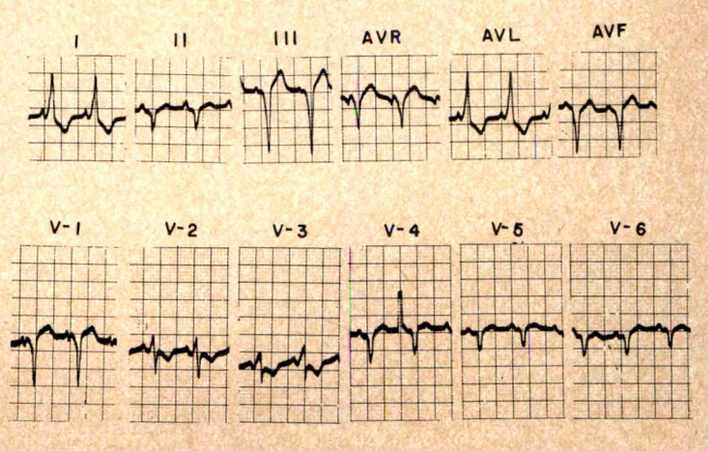

FIGURE 3. Electrocardiogram of November 9, 1960 demonstrating persistent preexcitation during sinus rhythm. Note the short P-R interval, wide QRS complexes and delta waves resembling those in Figure 2. See text for discussion.

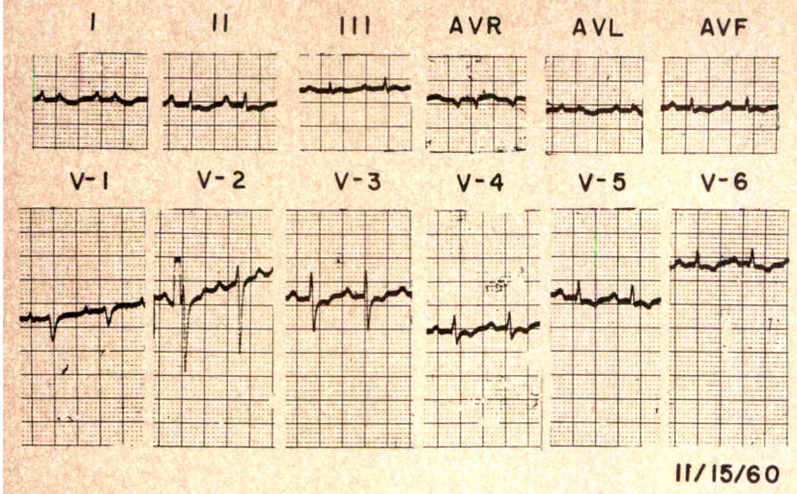

FIGURE 4. Electrocardiogram of November 15, 1960 demonstrating return to normal A-V conduction. Note the large P waves, low voltage of the QRS complex in the limb and left precordial leads and depressed S-T segment and inverted T waves in leads I to III and V_3 to V_6.

Pathologic Examination

Aside from the findings in the heart, the pathologic diagnoses were: (1) adenocarcinoma of the right breast with metastasis to (a) pancreas and celiac lymph nodes with obstruction of the pancreatic duct and common bile duct, and (b) left parametrium lymph nodes with obstruction of the left ureter; (2) bronchopneumonia with bilateral pleural effusion; and (3) osteoporosis.

Heart

The heart weighed 350 g. The pericardium was thickened throughout with tumor nodules visible in many areas. The right atrium and right ventricle were hypertrophied. The left atrium was dilated but normal in thickness. The tricuspid valve showed numerous aneurysmal dilatations. One part of the inferior leaflet of the mitral valve was longer than the remainder and had several aneurysmal dilatations. The sinuses of Valsalva of the pulmonary valve were dilated. The noncoronary aortic cusp likewise showed an aneurysmal dilatation and fenestration. The aortic sinuses of Valsalva were somewhat deepened.

Microscopic Examination

Methods

Both A-V rims were cut into blocks, and all blocks were serially sectioned and all sections retained. The sinoatrial (S-A) node and its approaches were serially sectioned and every 10th section was retained. The A-V node and its approaches, the A-V bundle, the left main bundle branch, and the first part of the right bundle branch were serially sectioned and all sections were retained. The remainder of the bundle branches up to the region of the moderator band was serially sectioned and every 10th section was retained. The remainder of the heart was cut into blocks and two sections were taken from each block. In the complete serial sections every fifth section was stained with Weigert-van Gieson and the remainder with hematoxylin-eosin stains. In all the other sections alternate sections were stained with hematoxylin-eosin and Weigert-van Gieson stains. In this manner 18,600 sections were examined. The findings were controlled by studies of the conduction system of normal hearts of various age periods.[3,4] This included 14 hearts from subjects aged 51 to 60 years for study of the sinoatrial (S-A) node, and 12 hearts from subjects in the same age group for the study of the A-V node, A-V bundle and bundle branches. These hearts showed no evidence of heart disease clinically, and were normal pathologically except for changes due to aging.

Findings

S-A node: There was considerable hemorrhage in and on the periphery.

Approaches to S-A node: Moderate arteriolar thickening was present. There was a marked chronic organizing pericarditis with masses of tumor cells, some of which were hyalinized. The myocardium itself showed considerable fibroelastosis.

Approaches to A-V node: There was marked fatty infiltration with diminution, but not complete destruction of the connections to the A-V node.

A-V node: No changes were noted. The normal fibers of James entered the terminal portion of the A-V node (Fig. 5). No abnormal A-V nodal bypass was found.

A-V bundle, penetrating portion: There was mild fatty infiltration and mild to moderate fibroelastosis.

A-V bundle, branching portion: This was very short and showed considerable fatty infiltration. The summit of the ventricular septum was abnormally formed. A portion of muscle was pinched off in one area although continuous with the ventricular septum elsewhere. This portion was engulfed by the branching bundle, with fibers of the bundle proceeding to the right and left side of the pinched off portion (Fig. 6). One group of bundle fibers consisting of about 6 to 10 cells joined this portion of the ventricular septum on its right side (Fig. 6). Just before the origin of the left bundle branch, another group of 5 to 10 bundle fibers proceeded downward into the main ventricular septum where several of the cells joined the ventricular septum (Fig. 7 to 9). Other fibers did not reach the ventricular septum.

Left bundle branch, main bundle: Moderate fatty infiltration and fibroelastosis were apparent.

Right bundle branch: At the origin of this branch there was marked fatty infiltration. Farther down there was slight fibrosis.

Left and right A-V regions: There were no bundles of Kent. Tumor masses were visible in the epicardium and beneath it in the A-V groove (Fig. 10).

Left ventricle: There was slight fibrosis and arteriolosclerosis.

Right ventricle: Marked fatty infiltration was present.

Ventricular septum: Focal fibrosis was noted.

Discussion

We[5] have previously pointed out that a proper histologic examination of the heart in a case of Wolff-Parkinson-White syndrome must include serial sectioning of both A-V rims and the conduction system. To date there are 16 reported cases of unquestioned Wolff-Parkinson-White syndrome in which this type of examination was performed.[5–18]

Previous Histologic Studies

In a neonate with Wolff-Parkinson-White syndrome (type undetermined) and an otherwise normal heart, Deerhake et al.[6] found a bundle of Kent in both the right and left A-V rings; the conduction system was normal. In a 21 month old child with Ebstein's disease with type B Wolff-Parkinson-White syndrome, Lev et al.[5] found (1) numerous bundles of Kent on the right side, (2) Mahaim fibers from the A-V bundle to the septum and from the right bundle branch to the septum, and (3) fibroelastosis surrounding the right bundle branch. In a 10 year old child with myocarditis and type B Wolff-Parkinson-White syndrome, Truex et al.[7] found a bundle of Kent on the right side and fibrosis of the A-V node and left bundle branch. In a 37 year old man with Chagas' disease and type B Wolff-Parkinson-White syndrome, Lev et al.[8] found (1) a bundle of Kent on the right side, (2) Mahaim fibers at the beginning of the left bundle branch, and (3) chronic inflammation at the approaches to the A-V node and in the A-V

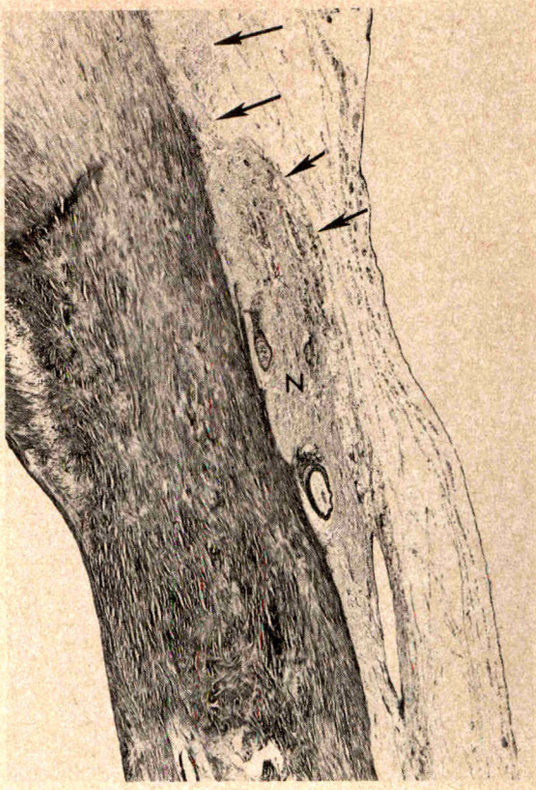

FIGURE 5. Normal fibers of James **(arrows)** entering the terminal portion of the A-V node (N). (Weigert-van Gieson stain ×17, reduced by 36 percent.)

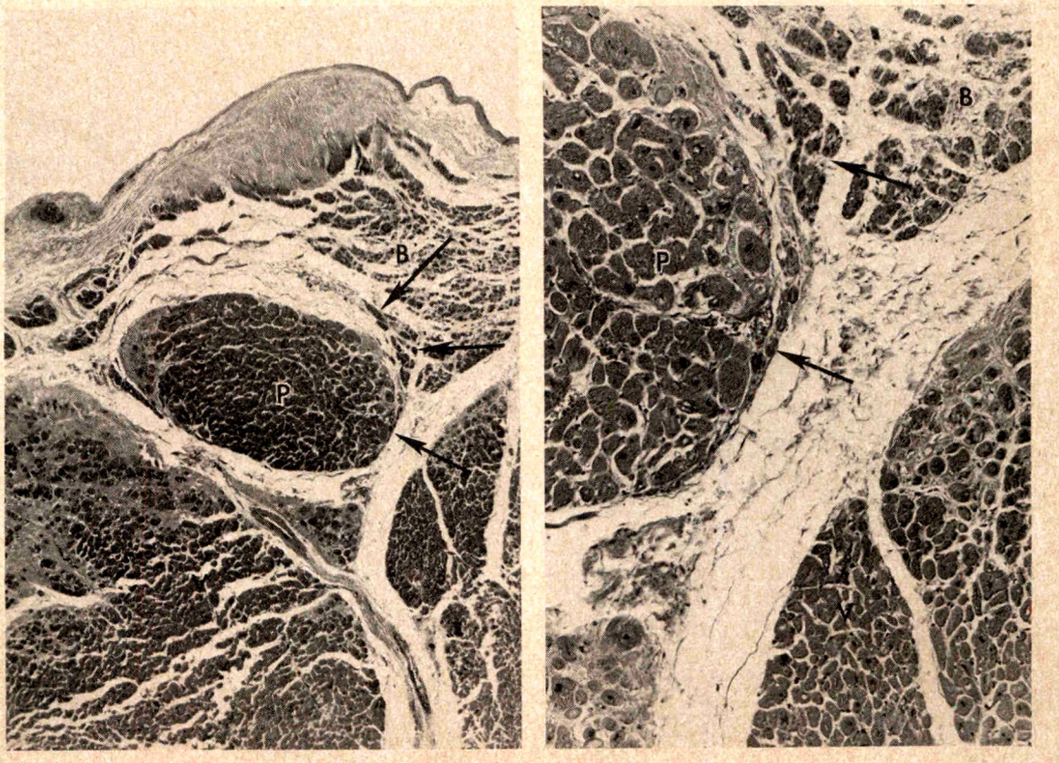

FIGURE 6. Summit of the ventricular septum, showing Mahaim fibers **(arrows)** surrounding pinched off portion of the ventricular septum (P) and joining the right side of the septum (V). B = A-V bundle. (Hematoxylin-eosin ×45 **(left)** and ×150, **(right)**, reduced by 36 percent.)

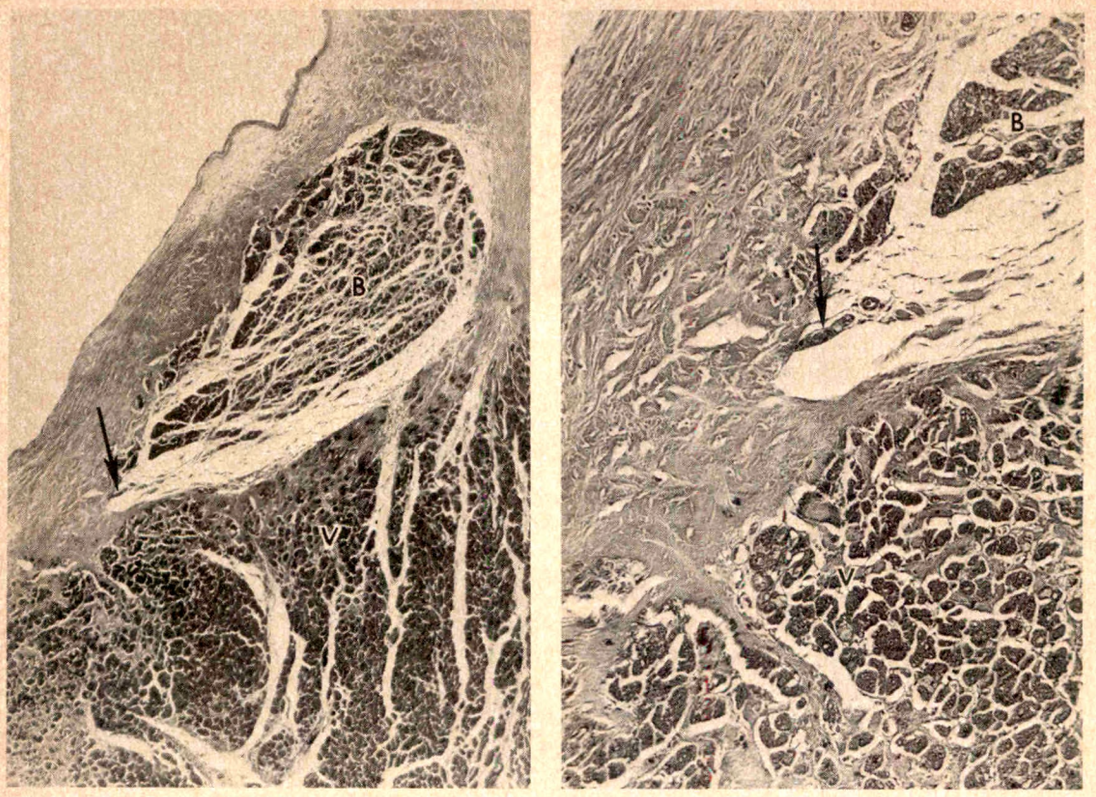

FIGURE 7. Fibers of Mahaim **(arrows)** passing, at the start of their course, to the left side of the ventricular septum (V). B = A-V bundle. (Hematoxylin-eosin ×45 **(left)** and ×150 **(right)**, reduced by 34 percent.)

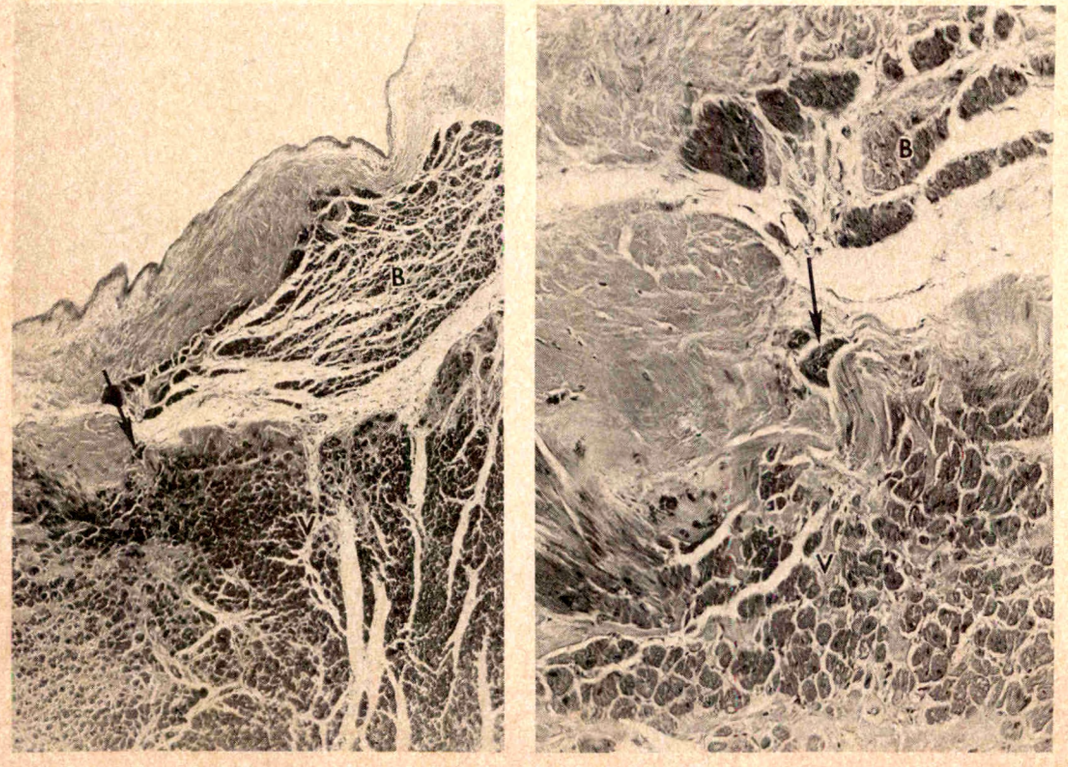

FIGURE 8. Further progress of Mahaim fibers **(arrows)**. (Hematoxylin-eosin ×45 **(left)** and ×150 **(right)**, reduced by 34 percent.) B = A-V bundle; V = ventricular septum.

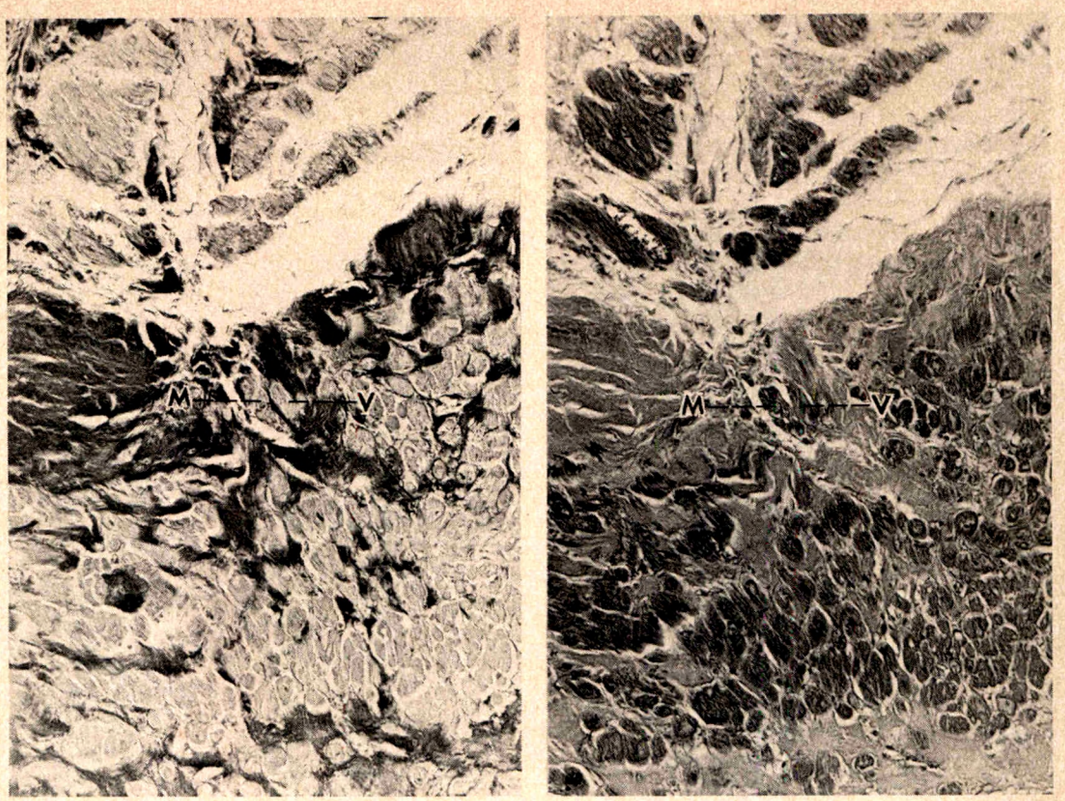

FIGURE 9. Termination of Mahaim fibers (M) in the ventricular septum (V). **Left,** just before termination. (Weigert-van Gieson ×150, reduced by 34 percent.) **Right,** termination. (Hematoxylin-eosin ×150, reduced by 34 percent.)

node, A-V bundle and bundle branches. In a 50 year old woman with arteriosclerotic heart disease with type B Wolff-Parkinson-White syndrome and incomplete left bundle branch block, Lev et al.[9] found (1) a bundle of Kent on the right side, (2) Mahaim fibers at the junction of the A-V node and A-V bundle and the ventricular septum, and (3) atrophy of the left bundle branch. In a 34 year old man with type B Wolff-Parkinson-White syndrome and A-V block with abnormal formation of the central fibrous body, Lev et al.[10] found (1) a tract proceeding from the atrial septum to the penetrating portion of the A-V bundle bypassing the A-V node, (2) copious Mahaim fibers from the A-V bundle to the ventricular septum, (3) no bundle of Kent, and (4) degeneration of the A-V bundle, bundle branches and the Mahaim fibers. In a dog with type A Wolff-Parkinson-White syndrome, Boineau and Moore[11] found a bundle of Kent on the posterior wall of the right ventricle close to the septum. In a 9 year old girl with a ventricular septal defect and type B Wolff-Parkinson-White syndrome, Rosenberg et al.[12] found a bundle of Kent on the right side and a normal conduction system. In a 3 1/2 year old girl with atypical Ebstein's disease and type B Wolff-Parkinson-White syndrome, the same authors[12] found a bundle of Kent on the right side and a normal conduction system.

In a 31 year old woman with mitral stenosis and

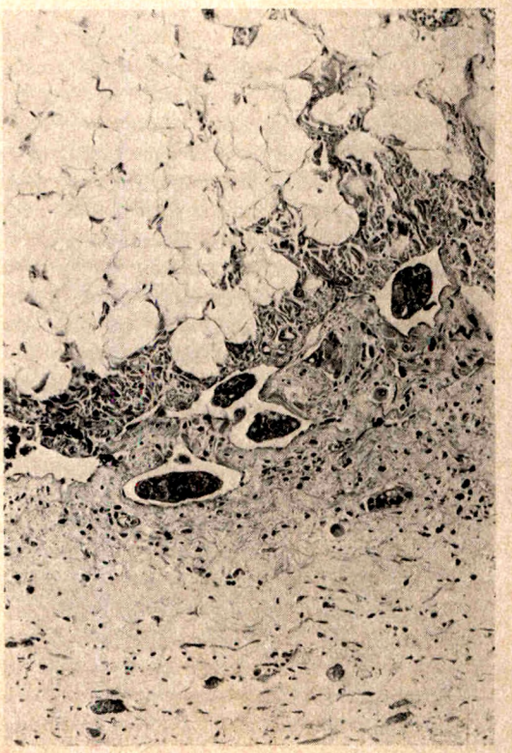

FIGURE 10. Tumor cells in epicardium. (Hematoxylin-eosin ×150, reduced by 40 percent.)

Wolff-Parkinson-White syndrome that changed from type A to type B, Lunel[13] found bundles of Kent in right anterior and right posterior sites and Mahaim fibers. In a 17 year old youth with a normal heart and type B Wolff-Parkinson-White syndrome, he[13] found a bundle of Kent in a right posterior site and Mahaim fibers. In a 15 year old boy with an otherwise normal heart and type A Wolff-Parkinson-White syndrome, Mann et al.[14] found two bundles of Kent on the left side and no Mahaim fibers. In a squirrel monkey with Wolff-Parkinson-White syndrome of the "bilateral" type, Boineau et al.[15] found a bundle of Kent in a right anterior site and another in a left anterior site. In a 56 year old woman with a normal heart and Wolff-Parkinson-White syndrome intermediate type between A and B, Brechenmacher et al.[16] found a bundle of Kent in the left posterior wall. There were no fibers of Mahaim. The S-A node showed fibrosis. In a 17 year old boy with idiopathic cardiomyopathy and three different patterns of excitation—type A with a short P-R interval, atypical type B with a slightly prolonged P-R interval and an intermediate type between A and B, Okada et al.[17] found a bypass tract from the A-V node to the ventricle, and two sets of Mahaim fibers, one from the proximal and one from the distal A-V bundle. In a 22 year old woman, with type A Wolff-Parkinson-White syndrome and extensive obscure disease of both atria, James and Puech[18] found (1) two bundles of Kent on the anterior part of the left ventricle, (2) an S-A node separated from the right atrium, (3) a crista terminalis replaced by fat, (4) focal degeneration in the internodal pathways, (5) the A-V node disconnected from the internodal pathways, with focal necrosis, (6) thickening of the S-A and A-V nodal arteries, (7) an abnormal central fibrous body, and (8) no connection between the His bundle and right bundle branch.

In addition, mention must be made of the work of Anderson et al.,[19] which introduced a possible new mechanism for the development of Wolff-Parkinson-White syndrome. In a 7 month old infant girl with mirror-image dextrocardia and inverted double outlet right ventricle with a variant of Wolff-Parkinson-White syndrome or Lown-Ganong-Levine syndrome, two nodes formed a common bundle that dipped directly into the ventricular myocardium and then bifurcated. Bundles of Kent were not looked for. Likewise Brechenmacher et al.,[16] in a 65 year old man with arteriosclerotic heart disease and Lown-Ganong-Levine syndrome and right bundle branch block, found auricular fibers penetrating into the bundle of His, fibrosis of the right bundle branch and degenerative lesions in the S-A node. Bundles of Kent were not looked for.

The preceding review reveals that from the anatomic standpoint, Wolff-Parkinson-White syndrome may be produced by (1) a bundle of Kent, (2) a tract from the atrial septum to the A-V bundle bypassing the A-V node with fibers of Mahaim, (3) the normal fibers of James with fibers of Mahaim, or (4) in complex congenital heart disease, two A-V nodes forming a common bundle with or without fibers of Mahaim. Lown-Ganong-Levine syndrome may be associated with auricular fibers connecting to the bundle of His, bypassing the A-V node, or the fibers of James bypassing the A-V node.

Types of Preexcitation

Electrocardiographically the following types of ventricular preexcitation are currently recognized: type A, type B and the Lown-Ganong-Levine syndrome. Type A is diagnosed when the delta wave and the remainder of the QRS complex are primarily upright in lead V_1 with this lead demonstrating R, RS, Rs, RSr and Rsr patterns. A positive delta wave is also seen in lead V_6. Type B is diagnosed when the delta wave and the QRS complex are negative in lead V_1 and this lead shows a Qs pattern and leads I and V_6 show a positive delta wave. In the Lown-Ganong-Levine syndrome only an abnormally shortened P-R interval is present without QRS prolongation by a delta wave. In general in type A there may be multiple posterior right or left anterior or posterior (or both) bundles of Kent, or A-V nodal bypass fibers and fibers of Mahaim. Type B usually represents right lateral ventricular preexcitation by way of a bundle of Kent. In the Lown-Ganong-Levine syndrome, as noted, one or more juxtanodal A-V bypass tracts may insert into the bundle of His.[20]

Type C preexcitation: On rare occasions a fourth type of preexcitation can be found, tentatively labeled by us type C (Pick A, unpublished observations). The characteristic features are seen in the precordial leads. The delta wave is negative (or isoelectric in leads V_5 and V_6 and positive in V_1 to V_4)—the opposite of the situation in type B. In the past 25 years we have encountered only two such cases, both in association with paroxysms of supraventricular tachycardia. Our interpretation postulates preexcitation forces directed from left to right due to a single accessory A-V bypass that subepicardially connects the left atrium with the lateral wall of the left ventricle. Although to our knowledge no such case has been completely studied anatomically, our assumption is supported by two cases of Wallace et al.[21] In both, left-sided lateral preexcitation was confirmed by extensive electrophysiologic studies and proved by successful surgical transection of the anomalous left-sided A-V connection; however, the authors presented the preoperative electrocardiograms in each case as a manifestation of type A preexcitation.

New variant of preexcitation: Examination of the electrocardiogram in our case revealed that the patient had intermittent preexcitation. The electrocardiogram on November 9, 1960 showed a short P-R interval, a delta wave and a wide QRS complex, the characteristic features of ventricular preexcitation. On all other occasions (with the exception of the electrocardiogram taken during atrial fibrillation), her tracings showed a normal P-R interval and narrow QRS complex. However, the QRS configuration during preexcitation conforms to no known pattern of

preexcitation, since it resembles neither type A nor type B. Thus, our case is an entirely new variant that does not fit into any current classification.[20]

James and Mahaim Fibers

The pathologic substrate in this case is the normally present James fibers, with Mahaim fibers passing from the A-V bundle to the left and to the right side of the posterior ventricular septum. By the term James fibers we mean those fibers of the atrium that insert on the end of the A-V node, just before it forms the penetrating portion of the bundle of His. One must postulate bypass of the A-V node by the fibers of James and simultaneous preexcitation of the ventricular septum and both ventricles directed anteriorly, posteriorly, laterally and apically. Breakthrough of the activation front at the site of the posterior right ventricle presumably produces the QS configuration in leads II, III and V_1. Breakthrough at the apex or the lateral wall of the left ventricle, or both, presumably produces the QS complexes in leads V_4 to V_6. Apparently during sinus rhythm the James and Mahaim fibers were functionally dependent, functioning either together or not at all. When the P-R interval shortened (A-V nodal bypass by way of James fibers) Mahaim tracts functioned, thus producing the very bizarre QRS complex. During the episodes of atrial fibrillation it is possible that Mahaim tracts functioned with or without participation of James fibers. In regard to the narrow QRS beats during atrial fibrillation, it cannot be definitely stated whether these were conducted by way of James fibers or the normal pathway, or both. However, the only moderately fast ventricular rate would suggest that the A-V node was involved in A-V conduction.

The manifestations of atrial fibrillation and flutter and enlarged P waves in the last electrocardiogram presumably reflected left atrial dilatation and carcinomatous infiltration of atrial epicardium. Chronic pericardial effusion can account for the low voltage of the QRS complex and the flat T wave inversions in the limb and chest leads. Reentrant paroxysmal tachycardia (utilizing bypass tracts) was never documented. The pathologic finding of aneurysmal dilatation of parts of the tricuspid and mitral valves and the arteriolosclerosis may have reflected injury related to radiation.

In a previous communication, we[10] demonstrated that Mahaim fibers may conduct when they are more than normally abundant. The current study indicates that normally present Mahaim fibers are facultatively conductive. However, in our case, the summit of the ventricular septum was abnormally formed, and this alteration may have played a role in the ability of Mahaim fibers to conduct. This finding was also present in our previous case.[10] Possibly, too, the presence of tumor in the atria, or the irradiation of the tumor, played a part in the stimulation or irritation of Mahaim fibers.

Our study also indicates the probability that the fibers of the atrial septum that insert on the end of the node (fibers of James) have the ability to bypass the node, as James[1] postulated. We know of no other explanation for the short P-R interval in our case.

Clinical Implications

Our case has important clinical implications. Since surgical ablation of anomalous pathways is feasible in selected patients with preexcitation and intractable arrhythmias,[21–23] the question arises whether surgical intervention would be appropriate in cases similar to the one presented. The presence of Mahaim fibers on both sides of the ventricular septum suggests that extensive surgical destruction of the upper septum would be necessary for total ablation of these fibers. Almost certainly this procedure would necessitate sectioning of the normal conduction system, resulting in complete A-V block (if accessory pathways were also successfully incised). In addition, epicardial mapping alone, although possibly suggesting septal preexcitation, would not suffice to locate accessory pathways. Bilateral intracardiac mapping would also be necessary for accurate localization of areas of preexcitation. The surgical problems inherent in cases such as this seem formidable at present.

Addendum

Since this paper was prepared, a new classification of fibers that might be important in ventricular preexcitation has been suggested (Anderson RH, Becker AE, Brechenmacher C, et al: Ventricular preexcitation. A proposed nomenclature for its substrates. Eur J Cardiol 3:27–36, 1975). In this proposed terminology, Kent fibers would be called accessory atrioventricular muscle bundles, Mahaim fibers coming from the distal part of the node would be called accessory nodoventricular muscle bundles, and those from the A-V bundle or left bundle branch, fasciculoventricular fibers. James fibers *as defined in this paper* would be named intranodal bypass tracts.

Acknowledgment

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Disappearance of Abnormal Q Waves After Aortocoronary Bypass Surgery

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Sixty-one patients were selected from 100 consecutive patients undergoing aortocoronary artery bypass. The number of vessels diseased as defined by coronary arteriography and the number of bypass grafts were recorded. Review of the preoperative electrocardiograms showed an infarct pattern in 26 of the 61 patients and analysis of the postoperative electrocardiograms revealed loss of abnormal Q waves in 3 of the 26. The pre- and postoperative clinical course of these three patients is analyzed and the extent of their coronary artery disease and number of bypass grafts compared with those of the 23 patients who had persistence of the infarction pattern and the 17 patients who manifested new Q waves. Possible explanations for the disappearance of abnormal Q waves are discussed.

Aortocoronary artery bypass with saphenous vein autograft or internal mammary artery is now widely performed in the management of some patients with angina pectoris. Several reports have described both symptomatic improvement and functional improvement by hemodynamic and exercise stress studies, as well as the status of the proximal and distal coronary arteries and of the graft itself. Postoperative electrocardiographic analyses have emphasized the significant incidence of new Q waves and conduction abnormalities[1–9]; the disappearance of abnormal Q waves after the bypass procedure has been postulated[8] but not definitively documented.

We report on three patients manifesting disappearance of abnormal Q waves within a few days after aortocoronary bypass. These Q waves had been present for months or years before the operation. One of these patients was studied postoperatively by cardiac catheterization and angiography, which revealed definitive hemodynamic improvement.

Material and Methods

One hundred consecutive cases of aortocoronary bypass performed at Mount Sinai Hospital were analyzed to ascertain the incidence of disappearance of pathologic Q waves in the postoperative period. The following criteria were used to select the patients: (1) single or multiple coronary artery bypass; (2) adequate preoperative and postoperative electrocardiograms; (3) absence of preoperative or postoperative left bundle branch block or new intraventricular conduction abnormalities; and (4) adequate follow-up for at least 6 months postoperatively. Patients who had aneurysmectomy along with the coronary artery bypass were excluded, but those with associated valvular surgery were included.

The selection criteria were met by 61 patients, 53 men and 8 women, with a mean age of 57 years. Their case records were analyzed to evaluate the number of vessels involved as demonstrated by coronary arteriography, the number of bypass grafts implanted, and the presence or absence of persistent abnormal Q waves in several pre- and postoperative electrocardiograms.

Three patients had postoperative disappearance of abnormal Q waves. Their clinical course and the results of postoperative cardiac catheterization,

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TABLE I

Vessel Involvement As Assessed by Coronary Arteriography

Vessels Involved (no.)	Patients (no.)	Previous MI	New Q Waves	Q Wave Loss	No QRS Change
1	15	5	1	2	12
2	31	13	10	1	20
3	15	8	6	0	9
Total	61	26	17	3	41

MI = myocardial infarction.

left ventriculography and coronary arteriography in one of them are included in this report. The number of vessels diseased and the number of bypass grafts performed were correlated with the electrocardiographic changes.

Four patients had procedures in addition to coronary artery bypass: Three had valve replacement (two mitral and one aortic) and one had coronary endarterectomy of two vessels before venous grafts were implanted.

Results

Analysis of the preoperative electrocardiograms revealed that 26 of 61 patients had evidence of a previous myocardial infarction (anterior in 5, inferior in 19 and inferolateral in 2).

Correlation of Q waves with extent of coronary disease and number of grafts: Fifteen patients had evidence of one vessel disease, 31 had two vessel and 15 had three vessel disease. At operation, 18 of these patients received one bypass graft, 30 received two grafts, 12 received three grafts and 1 received four grafts.

Seventeen patients (27.8 percent) had new Q waves after the bypass procedure. The pathologic Q wave disappeared after the operation in 3 of the 26 patients (11.5 percent) with a preoperative pattern of myocardial infarction in the electrocardiogram (Fig. 1 to 3).

Sixteen of 17 patients with new Q waves and 20 of 23 patients with persistence of the pattern of myocardial infarction were in the group with two or three vessel disease; 2 of the 3 patients with Q wave loss had one vessel disease and 1 had two vessel disease (Table I). Similar findings were noted when these data were correlated with the number of bypass grafts implanted; that is, 15 of 17 patients with new Q waves and 18 of 23 with a preoperative pattern of myocardial infarction had two or three bypass grafts, whereas none of the patients with Q wave loss had more than two grafts implanted.

Clinical course of patients with Q wave loss: The pre- and postoperative clinical course of the three patients whose abnormal Q waves disappeared after bypass grafting is shown in Table II. The age of these patients was considerably lower than the mean age of 57 years for the whole group. The preoperative myocardial infarction occurred 5 years before operation in Patient 2 and within 1 year of operation in Patients 1 and 3. All three patients were disabled by intractable angina at the time of referral for surgery, one (Patient 3) having attacks of typical Prinzmetal's angina. Patient 1 had paroxysmal episodes of cardiac failure, always associated with episodes of chest pain. None had documented ventricular arrhythmias. Patients 1 and 3 had one vessel disease and one bypass graft; Patient 2 had two vessel disease and two bypass grafts. Patient 2 had two operations: In the first, the left anterior descending coronary artery was bypassed; 2 years later, because of recurrent angina and demonstration of a left circumflex arterial lesion, a graft to the latter artery was implanted. After this second operation the abnormal Q waves in the electrocardiogram disappeared (Fig. 2).

These three patients had an uneventful postoperative course and were discharged in an angina-free

TABLE II

Data in Three Patients with Q Wave Loss Postoperatively

Case (no.)	Age (yr) & Sex	Vessel Involved	LV Angiogram	Bypass Grafts	Location of MI		Clinical Course	
					Preop	Postop	Preop	Postop
1	43M	LAD	Hypokinesis of antero-lateral wall	LAD (IMA)	Ant	None	MI 8 mo preop. Recurrent angina and two episodes of pulmonary edema.	Angina-free for 9 mo; then recurrence of stable angina. No heart failure
2	38M	LAD, LCx	Hypokinesis of anterior wall	LAD, LCx (SVG)	Ant	None	MI 5 yr preop.* First bypass to LAD 2 yr preop* with recurrence of angina 11 months later	Angina-free after bypass to LCx
3	53F	LAD	Hypokinesis of anterior wall	LAD (SVG)	Ant	None	MI probably 4 mo preop; then Prinzmetal's angina	Angina-free. Repeated angiogram: patent graft and normal LV contractility

* Period before second bypass (to left circumflex coronary artery).

Ant = anterior; IMA = internal mammary artery; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricular; MI = myocardial infarction; postop = postoperative; preop = preoperative; SVG = saphenous vein graft.

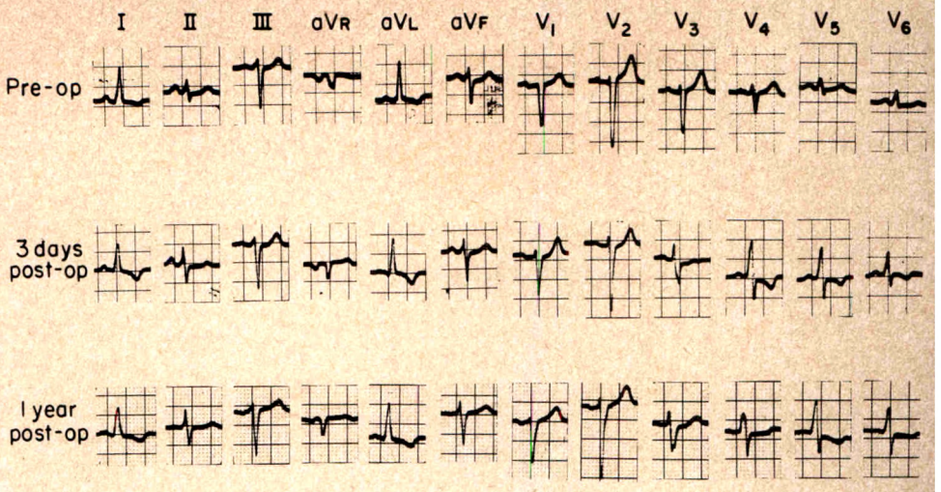

FIGURE 1. Case 1. Serial electrocardiograms demonstrating an anteroseptal myocardial infarction in the preoperative tracing **(top)** and appearance of an r wave in lead V_1 and disappearance of the tiny q wave preceding the R wave in lead V_2 in the two postoperative tracings.

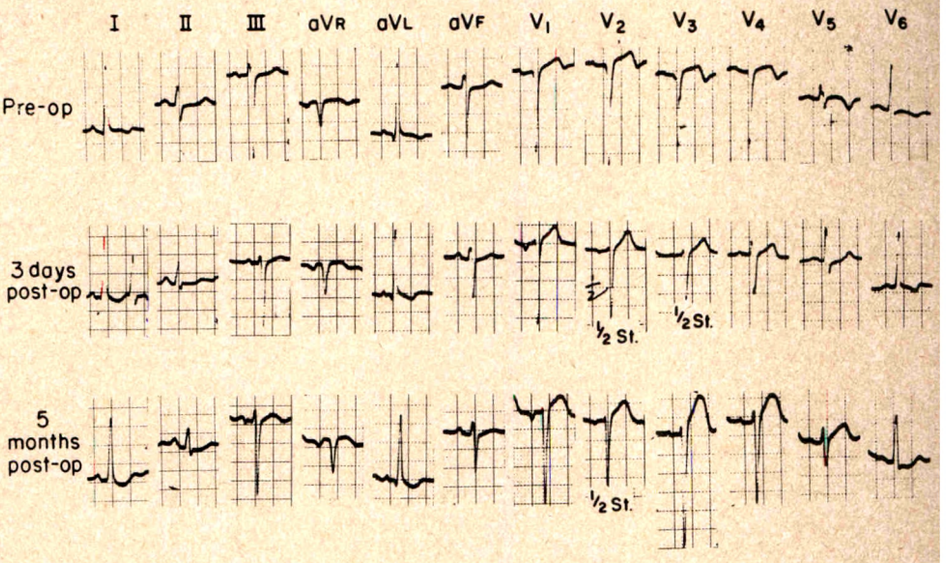

FIGURE 2. Case 2. Serial electrocardiograms demonstrating an anteroseptal myocardial infarction in the preoperative tracing **(top)** and appearance of r waves in leads V_1 to V_4 in the two postoperative tracings.

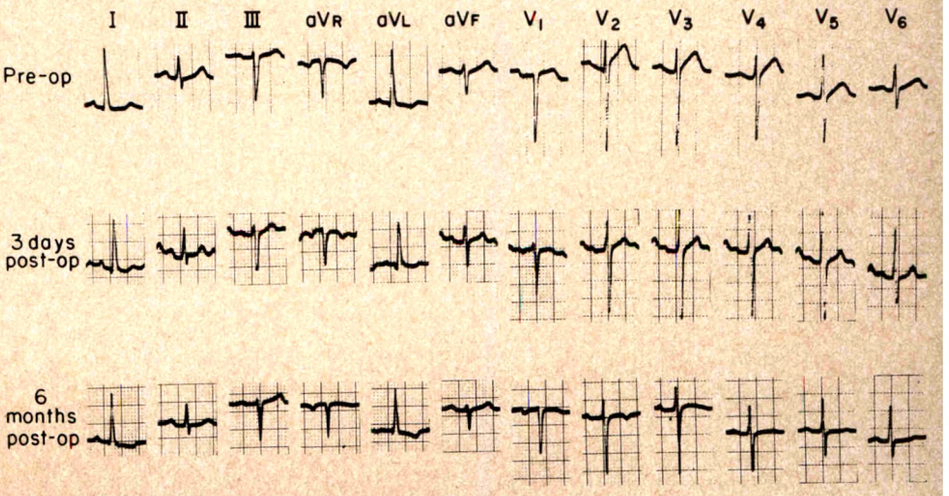

FIGURE 3. Case 3. Serial electrocardiograms demonstrating an anteroseptal myocardial infarction in the preoperative tracing **(top)** and appearance of an r wave in lead V_1 and disappearance of the q wave preceding the R wave in lead V_2 in the two postoperative tracings.

state approximately 3 weeks after the operation. Patients 2 and 3 have remained angina-free for 1 year and 14 months, respectively; Patient 1, who was free of angina for 9 months and then had recurrence of mild stable angina, has refused restudy. Patient 3 was restudied 4 months after the operation and was found to have a patent vein graft; the left ventricular end-diastolic pressure had improved from 23 to 11 mm Hg postoperatively and the left ventricular angiogram demonstrated normal wall contraction in a previously hypokinetic area.

Discussion

The increasing number of aortocoronary artery bypass procedures performed in patients with angina pectoris has stimulated cardiologists to evaluate critically the results of these operations. The occurrence of symptomatic improvement is widely recognized, but whether the procedure results in functional improvement and rehabilitation, prevents myocardial infarction or reduces mortality from coronary artery disease, are still controversial matters. Until long-term controlled studies are available these questions will remain unanswered.

New Q waves after bypass surgery: Several recent electrocardiographic and vectorcardiographic studies have indicated a high incidence rate of new Q waves after coronary artery bypass.[1–9] The interpretation of this finding has varied extensively. Espinoza et al.[1] found a higher incidence rate in patients with two or three vessel disease and two or three grafts, presumably those with more severe disease, but the postoperative clinical course and mortality in this group were not affected. Rose et al.[7] found a very good correlation between enzyme elevation and new abnormal Q waves, thus supporting the concept of myocardial damage, even though the clinical course of their patients did not differ from that of other patients in the group. Bassan et al.[8] interpreted these new Q waves as unmasking of an old infarction rather than new myocardial damage, on the basis of their review of pre- and postoperative left ventriculograms; they speculated that the unmasking of an old infarction could be due to improved coronary perfusion to ischemic areas opposite the area of infarction. Finally, the postulation that these new Q waves might be due to early closure of the bypass grafts has been seriously challenged since the report of Assad-Morell et al.,[9] who found no relation between patency of the grafts and development of new Q waves. Thus, the final explanation for the meaning of these electrocardiographic changes remains unknown.

Disappearance of old Q waves after bypass surgery: Q waves compatible with previous myocardial infarction are frequently found in the preoperative electrocardiogram of patients undergoing coronary artery bypass surgery, as demonstrated in 26 of our 61 patients. The incidence of preoperative myocardial infarction is probably greater since it is well established that electrocardiograms of patients with a previous myocardial infarction can revert to normal or near-normal under various circumstances.[10–21] The knowledge that normalization of the electrocardiogram can be part of the natural course of patients with myocardial infarction led us to review the literature (1) to define the temporal relation between the acute episode and normalization of the electrocardiogram, and (2) to analyze the different mechanisms involved and look for a reasonable explanation for the disappearance of abnormal Q waves after coronary artery bypass surgery.

When normalization of the electrocardiogram occurs, it is usually observed within 1 year of the myocardial infarction.[10–21] Kalfbeich et al.[15] found that in the majority of electrocardiograms showing disappearance of significant Q waves the change occurred within 2 years of infarction; the changes occurred in none after 6 years and was found within 1 month in only 6 of 775 patients. Goldman et al.[22] noted Q wave disappearance within several days and Haiat et al.[14] found the change within 48 hours and normalization of the tracing 6 days after the acute infarct. Even earlier disappearance of Q waves has been described in angina pectoris, Prinzmetal's angina, metabolic abnormalities, phosphorus poisoning, allergic reactions and during cardiopulmonary bypass.[23–31] However, under all of these circumstances the reports concerned transient Q waves.

The incidence of normalization of an electrocardiogram is greater in subendocardial than in transmural infarction (35 versus 10 to 15 percent, respectively[10–21]), and disappearance of the infarction pattern does not change the prognosis in relation to mortality. A contrasting view was presented by Gittler et al.[18] in 1951; they reviewed the electrocardiograms of 51 patients 1 year after transmural myocardial infarction and found only one patient with a normal tracing and three with an "almost" normal tracing.

Mechanisms of disappearance of abnormal Q waves. These included (1) Appearance of left bundle branch block or intraventricular conduction abnormalities.[13] (2) Occurrence of a second infarction, as in 2 of the 14 cases of Pappas,[13] in which the signs of an anterior infarction disappeared a few months after a fresh inferior infarction developed. This could have been due to a modification of the balance of electrical potentials.[14] (3) Shrinkage of the area of infarction with hypertrophy of the surrounding myocardium.[13,14] (4) Development of collateral circulation with improvement of perfusion of the infarcted area and its surrounding zone and increase of electrical activity in the so-called area of concussion.[24]

In our three patients with a preoperative electrocardiographic pattern of transmural myocardial infarction whose abnormal Q waves disappeared postoperatively, the changes occurred as early as 3 (Cases 1 and 3) and 7 (Case 2) days after operation. Although this finding could represent the natural course of myocardial infarction, as discussed, the temporal relation to the time of surgery suggests that it was related to the bypass procedure, particularly since the preoperative Q waves were present for 5 years in one patient (Case 2), about 1 year in Case 1 and at least 4 months in Case 3.

It is possible that the aortocoronary bypass, by increasing the perfusion of the areas surrounding the infarct and thereby improving the electrical activity of these myocardial cells, caused the disappearance of the abnormal Q waves in our patients. One of them was restudied postoperatively with demonstration of patency of the graft and improvement of left ventricular function and contractility, findings that can be assumed to be due to the increased perfusion made available by the venous bypass. Although the disappearance of angina in postoperative patients is not a definitive sign of improved coronary perfusion, the uneventful postoperative recovery of these patients and their return to full activity also suggests benefit from the bypass procedure. The observation that two of the three patients had only one vessel disease, whereas the majority of those who manifested new Q waves or persistence of the infarction pattern had two or three vessel disease, may imply a lesser degree of coronary artery disease.

The final explanation for the electrocardiographic changes after coronary artery bypass surgery, either the appearance of new Q waves or the disappearance of the myocardial infarction pattern, requires study of a larger series with correlation of the angiographic and electrocardiographic findings in the postoperative period.

Addendum

Since submission of this article, another report describing six patients with reappearance of anterior QRS electrical forces within 10 days of coronary arterial bypass surgery has been published (Zeft HJ, Friedberg HD, King JF, et al: Reappearance of anterior QRS forces after coronary bypass surgery. An electrovectorcardiographic study. Am J Cardiol 36: 163–168, 1975). In addition, a report of appearance and disappearance of transient Q waves in Prinzmetal's angina has also been published (Meller J, Conde CA, Donoso E, et al: Transient Q waves in Prinzmetal's angina. Am J Cardiol 35:691–695, 1975).

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Comparative Cardiac Dynamic Effects of Dobutamine and Isoproterenol in Conscious Instrumented Dogs

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The cardiac dynamic consequences were evaluated of constant infusions of dobutamine and isoproterenol at graded dose levels into conscious, healthy instrumented dogs. Measurements were made of simultaneous changes in left ventricular internal diameter, pressure, aortic pressure and rate of rise of left ventricular pressure (dP/dt), as well as the left ventricular electrogram. From these primary variables, derived variables were computed using programs in a minicomputer system. The data showed that, with increasing doses of dobutamine there were significant linear increases in all measured indexes of myocardial contractility, such as the rate of rise of left ventricular pressure at a developed isovolumic pressure of 40 mm Hg ($dP/dt/P_{40}$), mean velocity of left ventricular fiber shortening, ejection fraction and stroke work. These changes in myocardial contractility occurred without changes in end-diastolic volume, mean aortic pressure or heart rate when dobutamine was infused in doses of 5 to 20 μg/kg per min. Isoproterenol also produced linear changes in indexes of myocardial contractility but in doses of 0.02 to 0.10 μg/kg per min, it produced a significantly higher heart rate at any given level of contractility than that produced by dobutamine. Cardiac minute work (heart rate × stroke work) was increased by both drugs. However, with infusions of isoproterenol the amount of cardiac minute work was significantly limited because of the changes in heart rate, whereas with dobutamine cardiac minute work could be increased to a higher level as a function of changes in myocardial contractility alone without changes in heart rate. These data suggest that dobutamine selectively increases myocardial contractility.

Isoproterenol[1–5] and, recently, dopamine[6–8] have been the drugs of choice for restoration of cardiac function in patients with acute depression of myocardial performance after acute myocardial infarction, in the low cardiac output syndrome and during the postoperative period after cardiac surgery. A basic physiologic approach to therapy for myocardial dysfunction must involve the modulation of one or all of the determinants of cardiac performance.[9–13] The determining factors are end-diastolic myocardial fiber length, ventricular midwall tensile stress or afterload, and myocardial contractility. The drugs used most frequently[1–8] for improvement of cardiac performance act by increasing myocardial contractility in situations in which myocardial performance is acutely depressed. However, although infusions of these drugs increase myocardial contractility, they have adverse side effects, such as tachycardia, hypotension, hypertension and frequent occurrence of arrhythmia at effective dose levels.

The ability to change selectively the level of myocardial contractility without producing significant changes in preload, afterload, heart rate or rhythm has been difficult to achieve. Tuttle, Mills and coworkers[14–16] synthesized a new drug dobutamine, which is said to in-

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crease myocardial contractility selectively without producing arrhythmia, tachycardia or significant changes in preload and mean aortic perfusion pressure.[17,18]

We therefore compared the cardiac dynamic effects of graded infusions of dobutamine and those produced by isoproterenol in conscious instrumented dogs in which changes in end-diastolic volume, end-systolic volume, left ventricular pressure, mean aortic pressure, heart rate and other derived variables indicative of cardiac function could be monitored from beat to beat. These studies were designed to ascertain in conscious dogs which dynamic consequences resulted from increased myocardial contractility without changes in end-diastolic volume, mean aortic pressure and heart rate in contrast to increased myocardial contractility with such changes.

Methods

Instrumentation: The laboratory techniques for preparation of conscious instrumented dogs have previously been described.[19–22] Briefly, healthy dogs certified by a veterinarian after a 1 month quarantine period were given antibiotic agents prophylactically (Staphcillin®, 1 g/12 hours) for 2 days before operation. These dogs were premedicated with atropine sulfate, 1 mg/kg, and lidocaine hydrochloride, 200 mg intramuscularly. All dogs were anesthetized with Nembutal®, 30 mg/kg intraperitoneally. An open airway was maintained with a cuffed endotracheal tube in the trachea. After an aseptic surgical field was prepared, a left thoracotomy was performed in the fifth intercostal space. Respiration was maintained through intermittent positive pressure breathing of 60 percent oxygen and 40 percent room air. Continuous infusion of Ringer's lactate solution was given during the surgical procedure. The lungs were retracted. The pericardium was incised for its entire length from base to apex of the left ventricle. Butyn sulfate (2 percent) was applied to the surface of the heart. This substance provided epicardial anesthesia and reduced the incidence of surface irritability while the heart was being manipulated.

Implantation of transducing devices involved placement of a pair of coils in the plane of the minor semiaxis of the left ventricle for measurements of internal diameter and placement of implantable pressure transducers in the left ventricle and aorta. One pair of Teflon®-coated multistranded stainless steel wires was sutured into the ventricular wall. These bipolar electrodes were used to record the electrogram. After all gauges were placed on the heart and blood vessels, the pericardium was cleansed and closed with interrupted sutures. The relative positions of these transducing devices in the left ventricle and aorta are shown in Figure 1. Two to 3 weeks after recovery from surgery, control data were established for each animal. The conscious instrumented dogs were routinely studied while they stood quietly in a modified Pavlov stand. The dogs were trained and were able to remain comfortably in the stand for as long as 12 hours without becoming disturbed.

Measurement of left ventricular internal diameter: This diameter was measured using the technique of inductance micrometry.[22] This approach is based on the principle that when a closed conductive loop of fixed cross-sectional area is placed in a magnetic field, an electromotive force is induced in the loop and is dependent on the distance separating the loop from the magnetic field. The principal limitation of the application of this method is the inherent nonlinearity between output voltage and separation for such a system. In the system used in these studies, two small specially constructed wire-wound coils (Hazen Everett Co., Mahwah, N. J.) were placed on the endocardium. One coil was excited at a known frequency and voltage for the generation of a magnetic field. The second coil, placed diametrically opposite to and coaxial with the primary coil, had an induced electromotive force that was a linear function of the distance separating the primary and secondary coils. Each coil weighed approximately 500 mg, had a diameter of 6 mm and a thickness of 3 mm. A system designed in our laboratory provided all the electronic functions necessary to deliver the driver power, linearize and amplify the dimension signal, and calibrate the output from the inductance micrometers.

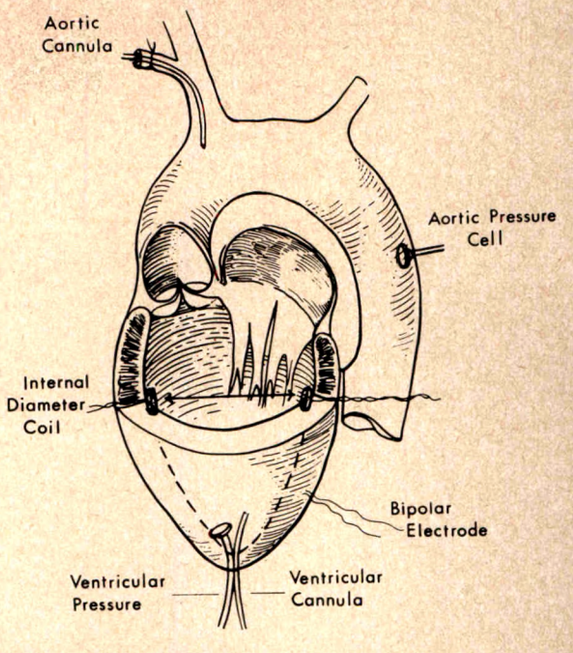

FIGURE 1. Schematic drawing showing the relative placement of gauges in the left ventricle and aorta.

Measurement of pressures: Implantable pressure transducers (Konigsberg Instruments, Inc., Pasadena, Calif.) and small polyvinyl tubes were used to measure pressure. The cells were usually 6.5 mm in diameter. The left ventricular pressure cell and a cannula were placed 3 cm into the left ventricular cavity. The same kind of cell was implanted in the aorta 1 cm distal to the subclavian artery. A small polyvinyl cannula was placed in the supraspinous artery and the tip placed into the aorta through the brachiocephalic artery. The cannulas and the lead wires from the transducers were brought out through the dorsum of the neck.

The cannulas were flushed with heparin daily for the first 2 weeks and then flushed twice weekly. Pressures were measured relative to atmospheric pressure by Statham P23DB strain gauges simultaneously with the pressures recorded from the pressure cells. This procedure was performed at the start and end of each experiment, to calibrate the pressure cells. The recordings system was very stable and permitted recording periods of up to 12 hours without drift. Appropriate adjustments in the calibration were made for large changes in barometric pressure when they occurred.

TABLE I

Control Data From 22 Conscious Instrumented Dogs

Variable	Mean	±	Standard Error
Weight (kg)	26	±	0.5
Days after surgery	74	±	18
Heart rate (beats/min)	99	±	4
Mean arterial pressure (mm Hg)	99	±	2
$dP/dt/P_{40}$ (sec^{-1})	76	±	4
Vcf (circumferences/sec)	1.7	±	0.1
End-diastolic volume (ml)	62	±	4
End-systolic volume (ml)	31	±	2
Stroke volume (ml)	31	±	2
Ejection fraction (%)	51	±	2
Stroke work (g/m)	49	±	3
$MDWF_{EJ}$ (g)	1712	±	79
TPR × 10^3 (dynes sec cm^{-5})	2.7	±	0.2

$dP/dt/P_{40}$ = rate of rise of left ventricular pressure at a developed pressure of 40 mm Hg; $MDWF_{EJ}$ = mean developed wall force during ejection; TPR = total peripheral resistance; Vcf = normalized mean velocity of left ventricular circumferential fiber shortening.

Calculation of left ventricular volumes: Changes in left ventricular volumes were determined from changes in the internal diameter of the left ventricle. It was assumed that the left ventricle was an ellipsoid of revolution with a fixed axis ratio of 1.5 during the cardiac cycle. Previous studies from our laboratory[19,21] have shown that reliable estimates of left ventricular volume (V_i) can be obtained from the equation ($V_i = 4/3\ \pi\ R_i^3 \times 1.5$), where R_i = internal radius. In addition, stroke volume estimated from dimensional changes correlates well with stroke volume as estimated by use of an electromagnetic flowmeter.[23]

$dP/dt/P_{40}$: The first derivative of the left ventricular pressure with respect to time was recorded with a Biotronex, model BL-620 active differentiator. The derivative was calibrated using the triangular wave technique. In these studies, the rate of rise of left ventricular pressure (dP/dt) at a developed pressure of 40 mm Hg during the phase of isovolumic contraction is used as an index of contractility. Studies by other investigators[24,25] as well as our own[26] show that $dP/dt/P_{40}$ (sec^{-1}) is not sensitive to changes in afterload or preload.

Mean Vcf and mean developed wall force during ejection: A second index of change in left ventricular myocardial contractility that we used was a change in the normalized mean velocity of left ventricular circumferential fiber shortening (mean Vcf) during ejection[26,27] at any given mean developed left ventricular internal wall force during ejection. Mean Vcf was calculated as follows:

$$\text{Mean Vcf (circumferences/sec)} = [2\ D_{ED} - D_{ES}]/[(D_{ED} + D_{ES})\ \Delta T]$$

where D_{ED} = end-diastolic left ventricular internal diameter; D_{ES} = end-systolic left ventricular internal diameter; and ΔT = ejection time in seconds.

Left ventricular internal wall force (g) was calculated from instantaneous changes in left ventricular pressure (g/cm^2) and the simultaneous equatorial left ventricular internal cross-sectional area (cm^2). These values were calculated by a computer from samples, taken at 5 msec intervals, of the primary variables, left ventricular internal diameter and pressure throughout a series of cardiac cycles.[19] The internal wall force, then, at any given 5 msec sampling period was equal to left ventricular pressure × $\Pi\ R_i^2$ for that period. The internal radius (R_i) was determined from the measurement of left ventricular internal diameter. Mean developed wall force during ejection (MDWF) was calculated as follows:

$$MDWF\ (g) = \bar{\chi}\ WF_{ej}\ (g) - WF_{ed}\ (g)$$

where $\bar{\chi}WF_{ej}$ = average wall force during ejection, and WF_{ed} = the wall force at end-diastole for that cycle.

Constant infusions: Infusions of dobutamine and isoproterenol were always made at a constant rate of 1 ml/min using a calibrated Harvard constant infusion pump. Infusions were always continued long after steady state conditions had been produced. Computer samples of the data representing the effect of a particular infusion concentration of these substances were usually taken 3 to 5 minutes after the onset of infusion during the steady state.

Data acquisition and reduction: With the transducers in place as described, their voltage outputs were cabled to the appropriate carrier, direct-current coupling and high and low gain amplifiers. The amplified and conditioned signals were then distributed, as required, by patch panel connections to (1) a recording system for permanent graph-

TABLE II

Cardiac Effects of Dobutamine in Conscious Dogs (mean ± 1 standard deviation)

Variable	Control	Dobutamine Infusions (μg/kg per min) 5.0	10.0	20.0	30.0
Heart rate (beats/min)	104 ± 7	100 ± 8	101 ± 25	106 ± 20	120 ± 16
Mean aortic pressure (mm Hg)	99 ± 14	103 ± 22	104 ± 17	108 ± 23	103 ± 26
$dP/dt/P_{40}$ (sec^{-1})	74 ± 19	91 ± 23	109 ± 28†	142 ± 36†	177 ± 40†
Mean Vcf (circ/sec)	1.57 ± 0.2	1.79 ± 0.3†	1.98 ± 0.4†	2.3 ± 0.6†	2.4 ± 0.5†
End-diastolic volume (ml)	68 ± 19	71 ± 19	69 ± 17	71 ± 19	70 ± 19
End-systolic volume (ml)	33 ± 10	32 ± 10	30 ± 10	28 ± 11	28 ± 11
Stroke volume (ml)	35 ± 9	39 ± 10	39 ± 9	43 ± 11	41 ± 11
Ejection fraction (%)	51 ± 5	55 ± 6	57 ± 8	61 ± 8	60 ± 8
TPR × 10^3 (dynes sec cm^{-5})	2.2 ± 0.5	2.1 ± 0.7	2.3 ± 1.0	1.9 ± 0.7†	1.6 ± 0.8†
Stroke work (g)	53 ± 11	67 ± 20	69 ± 17	84 ± 22†	83 ± 20†

* Each mean ± 1 standard deviation represents the mean ± standard deviation of the average value obtained from the study of seven dogs. For each individual dog, the 50 or more consecutive cardiac cycles were analyzed at steady state conditions to calculate the average value for each variable for that dog for each intervention.

† = Significantly different from control ($P < 0.01$).

$dP/dt/P_{40}$ = rate of rise of left ventricular pressure at a developed isovolumic pressure of 40 mm Hg; TPR = total peripheral resistance; Vcf = normalized mean velocity of left ventricular circumferential fiber shortening.

ic chart of analog signals, (2) a multichannel scope for monitoring and display, (3) an analog magnetic tape recorder for storage of all data signals, and (4) an analog to digital converter for input to the computer. In this mode, data can be sampled on-line; they can also be retrieved from magnetic tape for study and selection of portions for detailed processing by the computer, with 16K words of main memory (16 bit words) and two direct memory access channels, allowing data transmission rates up to 625 kilohertz by interleaving the channels. Peripheral devices include a multiplexed 16 channel, 14 bit resolution analog to digital converter capable of through put rates of 18 kilohertz; two moving head disc drives, each with a fixed disc and a removable cartridge providing a peripheral storage capability of 2.6 million words, accessible at a transfer rate of 45 kilohertz; a 7 channel digital magnetic tape unit (200 bits/inch, 30 inches/sec); a high speed printer (300 lines/min); and a Tektronix 4002A graphic terminal display unit. The hardware system is supervised by a HP-DOSM operating system with special input/output routines to facilitate continuous sampling and storage of large blocks of data (up to 500,000 words).

The Student's t test was used for pair group comparisons and a P value of less than 0.05 was considered to indicate a significant difference between compared groups of data.[28]

Results

Control data: The control data obtained from 22 conscious instrumented dogs are summarized in Table I. The dogs were studied 17 to 300 days postoperatively.

The cardiac effects of D-L dobutamine: D-L dobutamine was infused into seven conscious instrumented dogs in doses of 5, 10, 20 and 30 μg/kg per min intravenously. Table II shows the mean and standard error for each derived variable at each dose level. The control values for these variables did not differ from those in control animals. Analysis of these data shows that myocardial contractility was significantly increased as the dose of dobutamine was increased. Both $dP/dt/P_{40}$ and normalized mean Vcf were increased above the control level in each dog as the dose of dobutamine was increased. These changes occurred when there was no significant change in heart rate, end-diastolic volume or mean developed wall force or mean aortic pressure. At the higher dose levels (20 and 30 μg/kg per min), the calculated total peripheral resistance was significantly decreased, whereas stroke volume, stroke work and ejection fraction tended to increase and end-systolic volume tended to decrease. However, these changes were not significantly different from control values.

Cardiac effects of isoproterenol: Isoproterenol was infused into six conscious instrumented dogs so that the animals received 0.02, 0.04, 0.06 or 0.10 μg/kg per min of drug. Table III shows the mean and standard error for each variable during the control phase, as well as at each dose level. $dP/dt/P_{40}$ and heart rate increased at each dose level; there was no significant change in mean aortic pressure or mean developed wall force. End-diastolic and end-systolic volumes tended to decrease, whereas stroke volume increased. Mean Vcf and ejection fraction increased with increased doses, whereas stroke work gradually increased and total peripheral resistance decreased markedly with the infusions of isoproterenol.

Comparative cardiac effects of dobutamine and isoproterenol at a given level of contractility: The percent change from control value of various indexes when a given percent change in $dP/dt/P_{40}$ is produced by constant infusions of dobutamine and isoproterenol was calculated (Fig. 2). In such a plot, it is possible to compare the cardiac dynamic consequences of achieving a given state of contractility by infusions of dobutamine or isoproterenol. The first panel shows that for any given percent change in $dP/dt/P_{40}$ there is a resultant higher heart rate with isoproterenol than with dobutamine. Further, the level of total peripheral resistance is always significantly lower with isoproterenol than with dobutamine. Although the second panel shows no significant differences in the mean aortic pressure or end-diastolic volumes at any given state of contractility,

TABLE III

Cardiac Effects of Isoproterenol in Conscious Dogs (mean ± 1 standard deviation*)

Variable	Control	Isoproterenol Infusions (μg/kg per min)			
		0.02	0.04	0.06	0.1
Heart rate (beats/min)	99 ± 5	118 ± 10	138 ± 11	152 ± 11	161 ± 11
Mean aortic pressure (mm Hg)	101 ± 4	97 ± 5	94 ± 5	99 ± 6	92 ± 5
$dP/dt/P_{40}$ (sec^{-1})	78 ± 11	95 ± 13	109 ± 16	131 ± 18	134 ± 20
Mean Vcf (circ/sec)	1.9 ± 0.3	2.1 ± 0.26	2.2 ± 0.24	2.4 ± 0.24	2.4 ± 0.25
End-diastolic volume (ml)	64 ± 7	65 ± 9	61 ± 9	62 ± 9	58 ± 9
End-systolic volume (ml)	35 ± 6	31 ± 6	30 ± 6	29 ± 6	28 ± 5
Stroke volume (ml)	30 ± 2	33 ± 3	33 ± 4	33 ± 4	33 ± 4
Ejection fraction (%)	49 ± 3	53 ± 3	54 ± 3	55 ± 3	55 ± 2
TPR × 10^3 (dynes sec cm^{-5})	2.7 ± 0.14	1.9 ± 0.15	1.8 ± 0.23	1.6 ± 0.22	1.6 ± 0.22
Stroke work (g)	51 ± 4	56 ± 6	53 ± 7	59 ± 7	46 ± 8

* Each mean ± 1 standard deviation represents the mean ± standard deviation of the average value obtained from the study of six dogs. For each individual dog, the 50 or more consecutive cardiac cycles were analyzed at steady state conditions to calculate the average value for each variable for that dog for each intervention.

Abbreviations as in Table II.

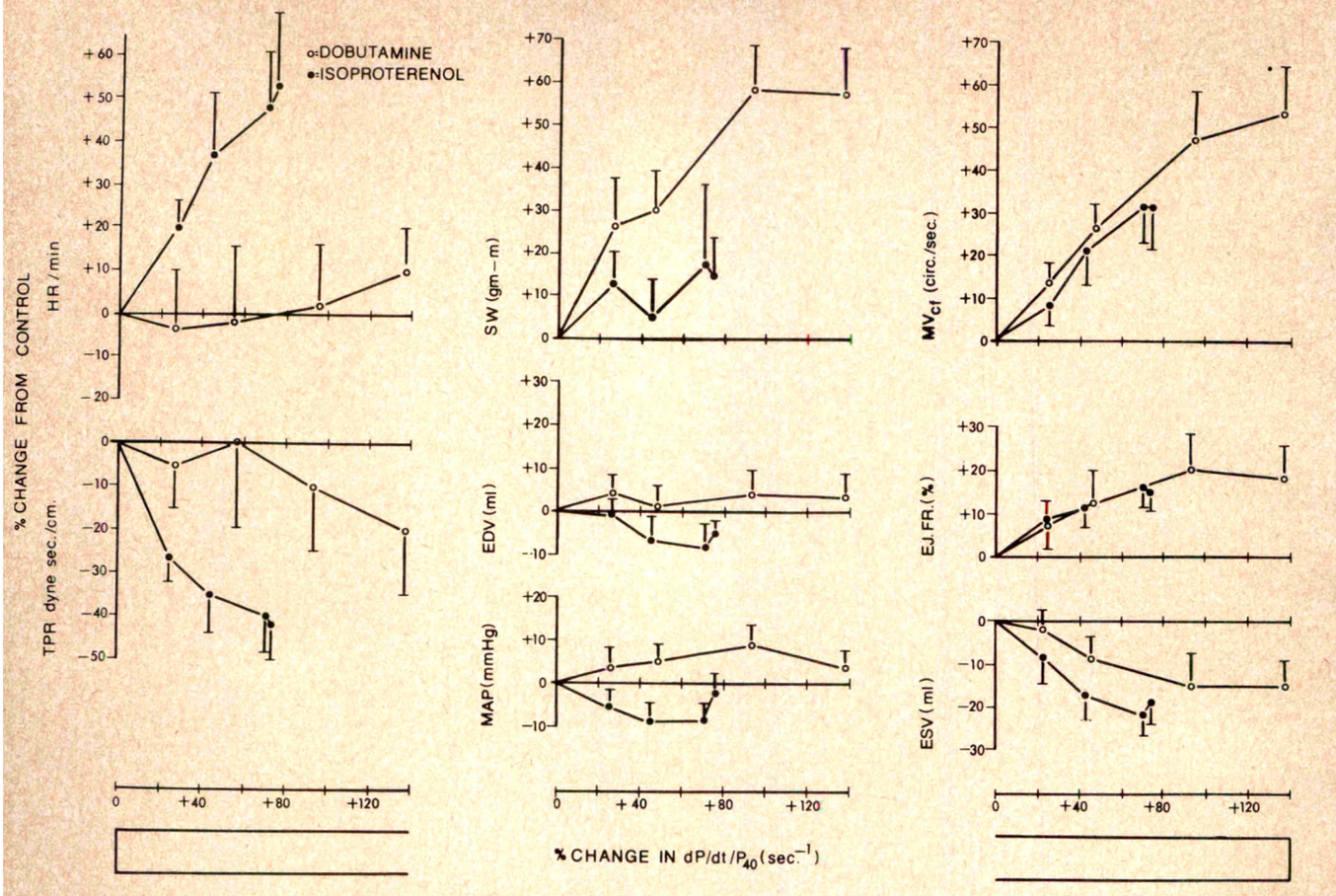

FIGURE 2. Graphs showing the percent change from control values of selected cardiovascular variables obtained for a given percent change in $dP/dt/P_{40}$ from control value when conscious dogs are given infusions of dobutamine (**open circles**) and isoproterenol (**closed circles**). Abbreviations as in Table I.

stroke work is greater for any given $dP/dt/P_{40}$ with dobutamine. The third panel shows that mean Vcf and ejection fraction increase linearly with each increase in $dP/dt/P_{40}$, whereas with isoproterenol there is a greater decrease in end-systolic volume from any given end-diastolic volume than with dobutamine. In addition, although, with isoproterenol, the changes in these variables tend to equilibrate at maximum after a 75 percent increase in $dP/dt/P_{40}$, with dobutamine, the maximal response in these same variables is seen only after $dP/dt/P_{40}$ has been increased up to 120 percent above the control level.

Effect of heart rate on ventricular function at a given level of contractility: Pacing ventricular function curves[21] were also used in conscious instrumented dogs to separate the relative contributions to alteration in cardiac performance of changes in ventricular rate changes and changes in contractility. As left ventricular rate is increased by pacing at increasing frequencies there is a linear decrease in end-diastolic volume and stroke work.[9,10,21] Further analysis of our data show that as pacing frequency increased and total cycle length decreased there was no significant change in $dP/dt/P_{40}$ ($r = 0.280$). Table IV shows the effect of changes in left ventricular rate on stroke work and $dP/dt/P_{40}$ for data files taken from three conscious dogs subjected to left ventricular pacing at respective rates of 2.4, 2.6 and 3.0 hertz during a control period. Cardiac minute work increased with increases in heart rate until there was a 40 percent change in heart rate. Beyond that point, the cardiac minute work decreased with further increases in heart rate.

Table V shows the mean and standard error for changes in cardiac minute work, stroke work and heart rate and $dP/dt/P_{40}$ that occurred in conscious dogs during constant infusions of dobutamine and isoproterenol. Cardiac minute work increased with both drugs. There was no significant change in heart rate with dobutamine, whereas $dP/dt/P_{40}$ increased as much as 100 percent. However, isoproterenol caused an increase in heart rate and, at any level of contractility, heart rate was higher with isoproterenol than with dobutamine. With a 40 percent change in $dP/dt/P_{40}$ from the control values the cardiac minute work was at a maximum, and this level appeared to be limited by the changes occurring in heart rate.

Discussion

Perhaps the primary physiologic objective in therapy of left ventricular myocardial dysfunction is to

TABLE IV

Effect of Ventricular Rate on Cardiac Minute Work in Conscious Dogs

Variable	Control	Frequency of Stimulation (hertz) 2.4	2.6	2.8	3.0
Cardiac minute work (g-m/min)	5189 ± 725	5804 ± 1812	5603 ± 1898	5303 ± 1992	4321 ± 161
Stroke work (g-m)	49 ± 5	39 ± 12	34 ± 12	30 ± 12	24 ± 1
Heart rate (beats/min)	105 ± 10	148 ± 1	160 ± 2	172 ± 1	183 ± 1
$dP/dt/P_{40}$ (sec^{-1})	83 ± 19	73 ± 5	69 ± 9	66 ± 6	66 ± 10

All values expressed as means ± standard deviation of the mean.
$dP/dt/P_{40}$ = rate of rise of left ventricular pressure at a developed isovolumic pressure of 40 mm Hg.

increase the cardiac minute work from any given end-diastolic volume at any given afterload against which a ventricle has to contract. The increase in cardiac minute work must be obtained at the lowest energy cost in terms of myocardial oxygen consumption ($M\dot{V}O_2$) and without compromising systemic and myocardial perfusion or significantly increasing the average midwall tensile stress during ejection.

Selective increases in myocardial contractility: Studies on isolated muscle and controlled experiments[9–13] have shown that one way to bring about a change in stroke work from any given end-diastolic volume and afterload is to increase selectively myocardial contractility. Selectively increasing myocardial contractility under these conditions will result in a decrease in end-systolic volume achieved from a given end-diastolic volume and thereby increase the stroke work. It has been difficult to increase selectively myocardial contractility in man or conscious animals using drugs such as catecholamines[2,6,8,29,30] without producing adverse side effects such as hypotension, hypertension, tachycardia and arrhythmia.

Infusions of dobutamine, a new catecholamine, have been reported[14–18] to stimulate $beta_1$ receptors of the heart and therefore cause selective increases in myocardial contractility. Our finding that constant infusions of dobutamine in conscious animals produced linear increases in all the measured indexes of myocardial contractility, such as $dP/dt/P_{40}$, mean Vcf, ejection fraction and stroke work, without changes in end-diastolic volume, heart rate and mean aortic pressure, confirms the conclusion that dobutamine selectively increases myocardial contractility in the conscious healthy dog. Further, the finding that end-systolic volume decreased while stroke volume and stroke work increased from any given end-diastolic volume shows that the cardiac dynamic effects of selectively increasing myocardial contractility are the same in the conscious animal as those predicted from studies in isolated cardiac muscle and classic controlled experiments.[9–13] In our studies, the changes in $dP/dt/P_{40}$ are considered synonymous with changes in myocardial contractility.

Effect of changing heart rate at a given level of myocardial contractility: Previous studies[9,10,21,31] have shown that increasing the rate of ventricular contraction by artificial stimulation decreases ventricular volume in conscious dogs. These studies demonstrated that stepwise increases in pacing rates from 2 to 3.5 hertz causes stepwise decreases in end-diastolic volume and stroke work without significantly altering myocardial contractility. Our finding that $dP/dt/P_{40}$ was not related to pacing rate further confirms the conclusion that increasing left ventricular rate does not change myocardial contractility. The ventricular function curve represents the relation between stroke work and end-diastolic volume produced through unique changes in ventricular rate at a given level of contractility. Further analysis of these data shows that cardiac minute work can be increased only up to a point through increases in heart rate alone. Our data show that when heart increases beyond 40 percent of the control rate there is a decrease in cardiac minute work at any given level of myocardial contractility. It is clear that the amount of cardiac minute work that can be produced by the left ventricle from any given level of end-diastolic volume and contractility is limited by the frequency of contraction of the left ventricle.

TABLE V

Effects of Dobutamine and Isoproterenol on Cardiac Minute Work

	CMW	SW	HR	$dp/dt/P_{40}$
Dobutamine (μg/kg per min)				
Control	5877 ± 220	53 ± 4	104 ± 3	74 ± 7
5.0	7360 ± 592	67 ± 8	100 ± 3	91 ± 9
10	7646 ± 914	69 ± 6	101 ± 9	109 ± 11
20	9972 ± 982	84 ± 8	106 ± 8	142 ± 14
30	11,199 ± 1097	83 ± 8	120 ± 6	177 ± 15
Isoproterenol (μg/kg per min)				
Control	4929 ± 381	51 ± 4	99 ± 5	78 ± 11
0.02	6460 ± 1534	56 ± 6	118 ± 10	95 ± 13
0.04	7366 ± 945	53 ± 7	138 ± 11	109 ± 16
0.06	7342 ± 1895	59 ± 7	152 ± 11	131 ± 16
0.10	7189 ± 1300	46 ± 8	161 ± 11	134 ± 2

All values expressed as means ± standard error of the means.
CMW = cardiac minute work (g-m/min); $dP/dt/P_{40}$ = rate of rise of left ventricular pressure at a developed isovolumic pressure of 40 mm Hg (sec^{-1}); HR = heart rate (beats/min); SW = stroke work (g-m).

Comparison of cardiac dynamic effects of dobutamine and isoproterenol: A comparison of the cardiac dynamic effects of dobutamine and isoproterenol can be equated to a comparison of the effects of changes in myocardial contractility and the effects of changes in both heart rate and myocardial

contractility. When a given level of contractility (60 percent change in $dP/dt/P_{40}$) was achieved by constant drug infusions, stroke work was increased by 40 percent with dobutamine but by only 10 percent with isoproterenol. However, cardiac minute work was increased by both drugs. The data show that minute work of the ventricle can be augmented in at least two ways: (1) through unique changes in myocardial contractility by which, at a given mean aortic pressure and end-diastolic volume, stroke volume, and thus stroke work, is increased; and (2) through an increase in heart rate and contractility by which, at a given mean arterial pressure, end-diastolic volume and stroke volume and the resultant stroke work are decreased, but the cardiac work per minute is increased. When a contractility level of 40 percent was reached through infusions of isoproterenol, a maximal increase in cardiac minute work was achieved; further infusions of isoproterenol were attended by further increases in heart rate and contractility but no further change in minute work. However, with infusions of dobutamine, cardiac minute work continued to increase with increases in contractility. It appears therefore that the absence of a chronotropic effect with infusions of dobutamine allows for greater increases in myocardial contractility and a greater amount of minute work from a given ventricle. That the reduced minute work obtained with isoproterenol is a function of the rate effect is supported by our data showing that at a given level of contractility cardiac minute work was dependent on the ventricular rate.

It is well known[32–35] that the major determinants of $M\dot{V}O_2$ are (1) myocardial stress, (2) the level of myocardial contractility, (3) heart rate, and (4) stroke work, which is said to be of minor importance as a determinant of MVO_2. Since at comparable levels of myocardial contractility, mean developed wall force and cardiac minute work, heart rate was always significantly higher with infusions of isoproterenol than with infusions of dobutamine, it can be assumed that the $M\dot{V}O_2$ must be greater with isoproterenol than with dobutamine because of the higher heart rate.[32] This conclusion is supported by the work of Tuttle et al.[14] They observed that, although both drugs produced coronary vasodilation, the coronary sinus partial pressure of oxygen (PO_2) was increased by 35 percent with dobutamine and decreased by 11 percent with isoproterenol when infusion of the two agents produced equal increases (68 percent) in myocardial contractility. This finding indicates that myocardial oxygen extraction was greater with isoproterenol than with dobutamine. Thus, dobutamine can be considered to increase myocardial oxygen availability through maintenance of myocardial perfusion pressure along with coronary vasodilation. The absence of a chronotropic effect with dobutamine further allows the ventricle to produce more minute work without compromising the balance between myocardial oxygen availability and myocardial oxygen demand.

Clinical implications: In patients with myocardial dysfunction, the functional muscle mass is reduced. To improve cardiac performance, there must be an increase in cardiac work from the existing functional cardiac muscle. Our studies show that this cardiac work can be increased through an increase in myocardial contractility alone or through increases in both heart rate and myocardial contractility. However, in the latter approach the amount of cardiac minute work that can be produced is limited by the frequency of contraction of the ventricle at any given level of contractility; thus, the change in heart rate that can be tolerated is of the utmost importance. It appears that the most effective way to increase cardiac minute work in myocardial dysfunction would be to increase myocardial contractility selectively at the lowest energy cost. From this vantage point, dobutamine would appear to be the more effective drug for treatment of myocardial dysfunction because it allows for marked increases in cardiac minute work through selective increases in myocardial contractility without changes in end-diastolic volume or mean developed wall force and at a lower energy cost because of the absence of a significant chronotropic effect.

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Effects of Ischemia and Coronary Reperfusion on Myocardial Digoxin Uptake

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The effects of coronary reperfusion on the uptake of digoxin by ischemic myocardium were studied in 17 open chest dogs undergoing anterior wall infarction produced by snaring confluent branches of the left coronary arterial system. Epicardial electrograms delineated ischemic, border and nonischemic zones. The hearts were reperfused by snare release after 1, 2 and 6 hours of occlusion. After 15 minutes of reperfusion, 1.0 mg of tritiated digoxin (^{3}H-digoxin) was given intravenously, and 2 hours later the hearts were excised and endocardial and epicardial samples from each zone were analyzed for ^{3}H-digoxin concentration. In another group of eight dogs regional myocardial blood flow was assessed utilizing 15 μ of radio-labeled microspheres administered during occlusion and reperfusion. In five dogs with 1 hour of coronary occlusion and subsequent reperfusion, ^{3}H-digoxin uptake was comparable in endocardial and epicardial layers of all three zones. In six dogs undergoing reperfusion after 2 hours of occlusion, mean ^{3}H-digoxin concentration was significantly ($P < 0.001$) reduced from the mean nonischemic concentration, by 54 percent in endocardial and 35 percent in epicardial layers of the ischemic zone. Border zone endocardial and epicardial ^{3}H-digoxin uptake was reduced by 21 percent and 16 percent, respectively ($P < 0.05$). In six dogs undergoing reperfusion after 6 hours of occlusion, ^{3}H-digoxin uptake in the ischemic zone was significantly ($P < 0.001$) reduced by 85 percent in endocardial and 60 percent in epicardial layers from the concentration in the nonischemic zone. Border zone uptake was decreased by 54 percent in endocardial and 36 percent in epicardial regions ($P < 0.01$). These alterations of in vivo digoxin binding could not be explained by impaired reflow of blood to ischemic myocardium. We conclude that coronary reperfusion after 2 to 6 hours of occlusion is associated with a marked reduction in myocardial digoxin uptake, which is more pronounced in subendocardial than in subepicardial regions of ischemic tissue.

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One of the essential functions of the myocardial cell membrane is the maintenance of physiologic cellular sodium (Na^+) and potassium (K^+) ion concentrations by active transport processes. There is convincing evidence that the mediator of active transport of Na^+ and K^+ is a membrane-bound, Na^+- and K^+-activated adenosine triphosphate phosphohydrolase enzyme complex that is thought to function as a "sodium pump."[1] However, only limited information is available concerning possible alterations in this myocardial ($Na^+ + K^+$)-adenosine triphosphatase complex after myocardial ischemia[2] or hypoxia[3] and the role, if any, of these changes in the pathogenesis of irreversible ischemic injury of the myocardial cell.

($Na^+ + K^+$)-adenosine triphosphatase activity and monovalent cation transport are specifically inhibited by digitalis glycosides,[4–6] and several investigators have suggested that this enzyme system

is the pharmacologic receptor for digitalis glycosides.[4–11] We[12] previously demonstrated that after 1 hour of coronary occlusion, there was substantial impairment of uptake of tritiated digoxin (^{3}H-digoxin) by ischemic myocardial tissue, which was greatest in regions of most severe ischemic injury as judged by changes in epicardial electrograms.

The experiments described herein were performed to determine the effect of coronary reperfusion after various periods of occlusion on the ability of the myocardium to bind ^{3}H-digoxin, a process thought to be related to the integrity of the ($Na^+ + K^+$)-adenosine triphosphatase system.[9,10] Regional blood flow measurements during identical periods of occlusion and reperfusion were made to determine the extent to which altered glycoside binding might be related to flow.

Methods

Myocardial uptake of ^{3}H-digoxin was measured in three groups of dogs after various periods of coronary occlusion and reperfusion. Animals were anesthetized with intravenously administered sodium pentobarbital (30 mg/kg), after which left thoracotomy was performed. Respiration was maintained with a positive pressure respirator (Bennett Respiratory Products, Inc., Santa Monica, Calif.). All animals breathed 40 percent oxygen throughout the experiment. The heart was suspended in a pericardial cradle, and snares were placed upon multiple confluent branches of the left anterior descending and circumflex coronary arterial systems supplying an area of anterior wall and apex of the left ventricle (Fig. 1).

For each dog, 10 to 12 mapping areas were designated on the epicardial surface of the left ventricle. Epicardial electrocardiographic mapping at each site was performed utilizing a stainless steel cylinder 8 cm long and 2.5 mm in diameter, the tip of which was smoothly ground and polished. The cylinder was attached to the exploring electrode of a conventional electrocardiographic lead system. This electrode was held lightly at a right angle to the epicardium during the surface mapping procedure. Epicardial electrograms were standardized at a stylus deflection of 1 mm/mv.

A femoral artery was isolated and a catheter passed into the central aorta. Arterial pressure was monitored with a Statham P23Db pressure transducer. Both arterial pressure and electrocardiographic recordings were made on a two channel Sanborn recorder at a paper speed of 50 mm/sec.

Experimental infarct model: After control recordings were obtained, serial coronary arterial branch occlusions were performed at 10 to 15 minute intervals until approximately one third to one half of the anterior surface of the left ventricle appeared cyanotic. This required from three to five ligatures. Adjacent coronary venous branches remained intact. After ligations were completed, surface mapping was again performed at the site previously mapped during the control period. Postocclusion electrograms revealed four zones (Fig. 1): (1) a central zone of ischemia characterized by S-T segment elevation or, occasionally, by S-T segment depression greater than 1 mv; (2) a peripheral ischemic zone showing qualitatively similar S-T segment changes of lesser magnitude; (3) a border zone 1.0 to 1.5 cm in width adjacent to the peripheral zone of ischemia, usually exhibiting S-T segment depression; and (4) a nonischemic zone within which S-T segments were unchanged from the control tracings.

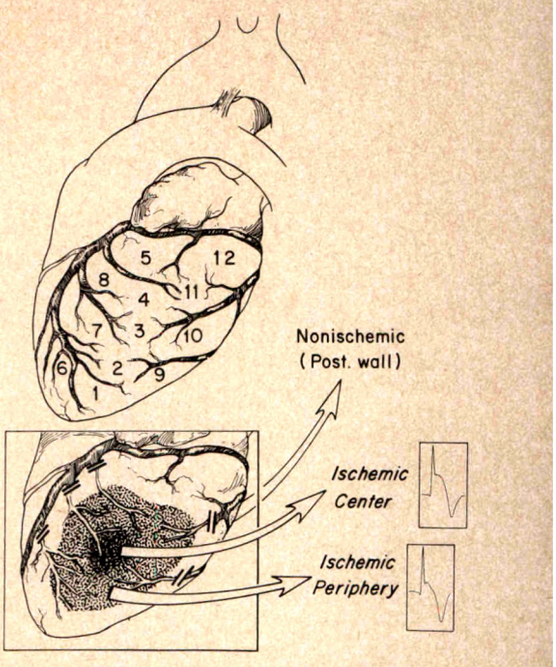

FIGURE 1. Diagramatic representation of the canine heart. **Upper drawing,** 12 epicardial mapping sites on the anterior surface of the left ventricle. **Lower drawing,** acute infarction produced by snaring multiple branches of the left anterior descending and circumflex coronary arteries. Central and peripheral zones of ischemia **(darkly shaded area)** are characterized by S-T segment elevation. Epicardial electrographic complexes were taken from a representative dog in this study. Post = posterior.

Reperfusion studies: The uptake of ^{3}H-digoxin after acute ischemia and reperfusion was examined in 17 open chest dogs undergoing anterior wall infarction in the manner described. Reperfusion was performed by snare release 1 hour (five dogs) or 2 or 6 hours (six dogs each) after occlusion. After 15 minutes of reperfusion, 1.0 mg of ^{3}H-digoxin (specific activity 143 μCi/mg)* was given intravenously and 2 hours later the hearts were excised and endocardial and epicardial samples from each zone were analyzed for concentration of ^{3}H-digoxin.

Myocardial ^{3}H-digoxin measurements: The method utilized for measuring left ventricular ^{3}H-digoxin uptake was as previously described.[12] Briefly, left ventricular endocardial and epicardial samples were blotted dry, washed, weighed and immediately refrigerated at −20° C. Within 2 weeks the specimens were thawed, diced and placed into vials containing 15 ml of the liquid scintillation medium described by Bray.[13] After vigorous shaking for 48 hours at 37° C to elute ^{3}H-digoxin from the samples, the contents of the vials were counted in a liquid scintillation spectrometer. Completeness of elution of ^{3}H-digoxin was assured by comparisons with samples fully solubilized with NCS (Amersham/Searle, Des Plaines, Ill.). Quenching correction was achieved by addition of internal standards of ^{3}H-digoxin.

Regional blood flow studies: Regional myocardial blood flow to ischemic and nonischemic myocardium during occlusion and reperfusion was measured in eight dogs, four with 2 hours and four with 6 hours of occlusion, utilizing 15 ± 5μ (mean ± standard error of the mean) carbonized radioactive microspheres (3M Company, Minneapolis,

* Kindly donated by Dr. Stanley T. Bloomfield, Burroughs Wellcome Co.

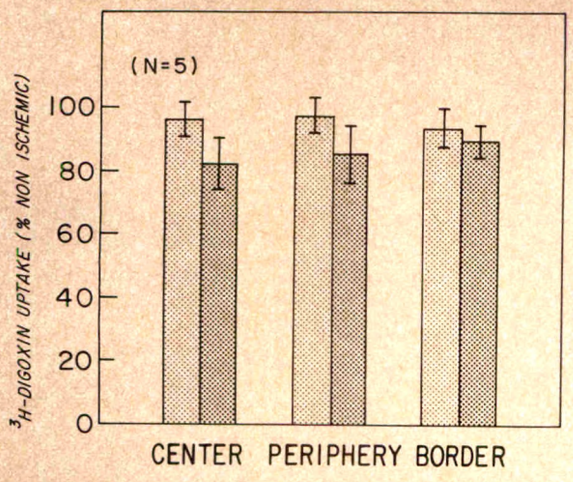

FIGURE 2. ^{3}H-digoxin uptake after coronary reperfusion in five dogs with 1 hour of coronary occlusion. Values are expressed as percent of nonischemic concentration in epicardial **(lightly stippled bars)** and endocardial **(darkly stippled bars)** halves of myocardial samples from the center **(left)** and peripheral **(middle)** zones of ischemia and from the border zone **(right)**.

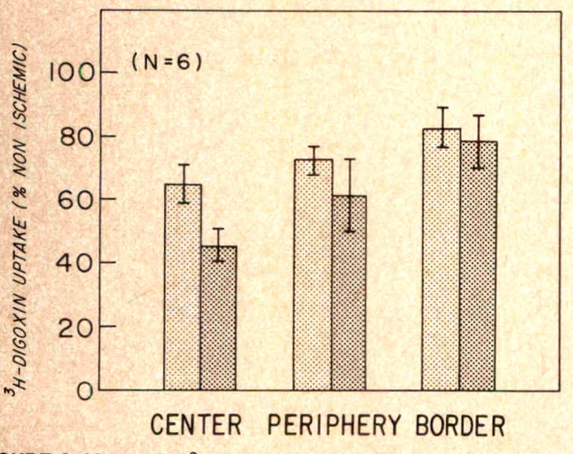

FIGURE 3. Myocardial ^{3}H-digoxin uptake after coronary reperfusion in six dogs with 2 hours of coronary occlusion. Conventions as in Figure 2.

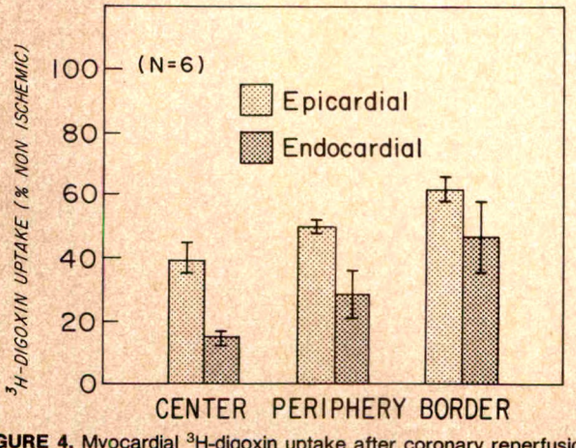

FIGURE 4. Myocardial ^{3}H-digoxin uptake after coronary reperfusion in six dogs with 6 hours of coronary occlusion. Conventions as in Figure 2.

Minn.). The microspheres were suspended in 10 ml of 10 percent dextran with 1 drop of Tween 80 added to minimize clumping. A bolus injection of 400,000 microspheres labeled with strontium-85 was made into the left atrium at the end of each occlusion period, 5 minutes before reflow. After 15 minutes of reperfusion, another bolus injection of microspheres labeled with cerium-141 was administered in the identical manner. This dose of microspheres has been shown to produce no alteration in systemic hemodynamics. Before a dose was withdrawn, vials containing the microspheres were dispersed in a Vortex mixer set at full speed for 5 minutes and then agitated in an ultrasonic bath for another 10 minutes. The resultant suspension appeared as a homogeneous, clump-free suspension of black microspheres. After the second injection of microspheres, the hearts were rapidly excised. Myocardial specimens from ischemic and nonischemic zones were divided into endocardial and epicardial halves as previously described in the studies of ^{3}H-digoxin uptake. The weighed tissue samples were placed in plastic tubes and counted in a gamma well scintillation counter (Nuclear Chicago) at two appropriately selected energy windows. Observed ^{85}Sr and ^{141}Ce counts were corrected for counting efficiency and channel overlap, and the rate of disintegrations/minute per gram for each nuclide was calculated.

Statistical analysis: All data are presented as mean values ± standard error of the mean; the significance of differences was assessed by the paired t test, each heart serving as its own control, using a two-tailed distribution.[14]

Results

Digoxin binding after coronary occlusion and reperfusion: ^{3}H-digoxin concentrations in endocardial and epicardial samples of ischemic, border and nonischemic myocardial zones after coronary reperfusion for dogs occluded for 1, 2 and 6 hours are shown in Figures 2 to 4. In the five dogs with 1 hour of occlusion and subsequent reperfusion (Fig. 2), ^{3}H-digoxin uptake was not significantly reduced in endocardial or epicardial halves of the central ischemic zone. Transmural ^{3}H-digoxin distribution as assessed by endocardial/epicardial ratios was comparable in all four zones.

In six dogs undergoing reperfusion after 2 hours of occlusion (Fig. 3), ^{3}H-digoxin concentrations in the center of the ischemic zone were significantly reduced (P <0.001) to 46 ± 5 percent of the nonischemic concentration in endocardial regions and to 65 ± 6 percent in epicardial regions. Mean ^{3}H-digoxin concentration in the periphery of the ischemic zone was significantly reduced to 62 ± 11 percent of the nonischemic concentration in endocardial regions and 82 ± 11 percent in epicardial regions (P <0.001). Border zone uptake was slightly decreased to 79 ± 9 percent of nonischemic uptake in endocardial layers and 84 ± 6 percent in epicardial layers (P <0.05).

In six dogs with reperfusion after 6 hours of occlusion (Fig. 4), ^{3}H-digoxin concentration in the center of the ischemic zone was markedly reduced to 15 ± 2 percent of the nonischemic concentration in endocardial regions and to 40 ± 4 percent in epicardial regions (P <0.001). The mean endocardial/epicardial ratio of ^{3}H-digoxin uptake in the center of the ischemic zone was 0.40 ± 0.04, compared with 1.07 ± 0.04

in nonischemic myocardium. In the periphery of the ischemic zone mean endocardial and epicardial ^{3}H-digoxin uptake was also significantly reduced to 28 ± 7 percent and 50 ± 2 percent, respectively (P <0.001), relative to concentrations in nonischemic myocardium. Border zone uptake was significantly decreased to 46 ± 11 percent of nonischemic uptake in endocardial layers and to 64 ± 4 percent in epicardial layers (P <0.001). Mean endocardial/epicardial ratios in the periphery of the ischemic and border zones were reduced to 0.59 ± 0.15 and 0.78 ± 0.17, respectively.

Thus, coronary reperfusion instituted after 2 and 6 hours of occlusion was associated with impairment of ^{3}H-digoxin uptake, which was greater the longer the period of occlusion before reflow. In addition, subendocardial concentrations of ^{3}H-digoxin were reduced to a significantly greater extent than were subepicardial concentrations, as demonstrated by the reversal of the endocardial to epicardial gradients observed in nonischemic tissue.

Regional blood flow during occlusion and reperfusion: To determine whether impaired reflow of blood to ischemic myocardium after reperfusion could account for the observed altered binding of ^{3}H-digoxin, further experiments were carried out to assess regional blood flow during occlusion and reperfusion after similar periods of ischemia. Table I shows regional flow measurements, expressed as percent of nonischemic flow, in eight dogs subjected to 15 minutes of reperfusion after either 2 or 6 hours of coronary occlusion. In four dogs with 2 hours of occlusion, regional flow at the end of the occlusion period was significantly reduced in endocardial and epicardial layers of ischemic and border zones. In the center of the ischemic zone, regional flow values were reduced to 6 percent (range 1 to 13 percent) of nonischemic flow values in endocardial layers and to 23 percent (range 11 to 27 percent) in epicardial layers. After reperfusion, flow values were restored to 209 percent (108 to 278 percent) and 206 percent (78 to 345 percent) in endocardial and epicardial layers, respectively, indicating transmural reactive hyperemia in this area. Qualitatively similar findings were observed in ischemic peripheral and border zone regions (Table I). In all animals, reperfusion of these areas resulted in restoration of regional flow equal to or greater than flow in nonischemic myocardium.

In four dogs with 6 hours of coronary occlusion (Table I), regional flow at the end of the occlusion period was also greatly reduced in ischemic myocardium. In the center of the ischemic zone, mean flow values decreased to 2 percent (0.3 to 5 percent) of nonischemic flow values in endocardial layers and to 18 percent (1 to 43 percent) in epicardial layers. After 15 minutes of reperfusion, regional flow values returned to 79 percent (31 to 131 percent) of nonischemic flow values in endocardial and 119 percent (34 to 197 percent) in epicardial regions, but a wide variation in flow recovery was manifest. Dog 5 had the smallest decrement in flow during the occlusion period and demonstrated the greatest degree of flow recovery during reperfusion. In the other three dogs in this group, the "no reflow" phenomenon was evident to various degrees (Table IB). At the time of sacrifice, subendocardial hemorrhage was grossly visible in these three animals. Regional flow patterns during occlusion and reperfusion in the periphery of the ischemic zone and in the border zone in this group were similar and showed complete or almost complete return to nonischemic values in three of the four dogs. Thus, after 6 hours of coronary occlusion, reperfusion resulted in impaired reflow of blood to ischemic myocardium. However, in three of four animals, flow was restored to greater than 75 percent of nonischemic values, indicating only a mild degree of "no reflow." However, despite this substantial recovery of passive flow, ^{3}H-digoxin uptake studies in dogs with 6 hours of occlusion and 15 minutes of reperfusion had a mean concentration of the glycoside in the center of the ischemic zone that was markedly reduced, to 15 percent of nonischemic concentration in endocardial regions and to 40 percent in epicardial regions. Results of the microsphere experiments

TABLE I

Regional Myocardial Blood Flow Represented as Percent of Nonischemic Flow in Dogs Undergoing 15 Minutes of Reperfusion (R) After 2 or 6 Hours of Occlusion (O)

		Epicardial		Endocardial	
Dog no.	Site	O	R	O	R
	A. Dogs with 2 Hours of Occlusion				
1	C	11	244	1	220
	P	13	242	11	121
	B	38	110	5	98
2	C	27	78	7	108
	P	34	104	9	137
	B	25	86	16	171
3	C	27	345	4	232
	P	54	111	28	227
	B	72	111	51	110
4	C	26	156	13	278
	P	33	112	15	281
	B	38	117	34	163
Mean values	C	23	206	6	209
	P	33	142	16	191
	B	43	106	26	135
	B. Dogs with 6 Hours of Occlusion				
5	C	43	137	6	131
	P	54	150	24	119
	B	58	135	39	96
6	C	24	197	0.5	77
	P	33	243	1	156
	B	66	132	40	155
7	C	1	34	0.3	31
	P	3	38	2	45
	B	52	118	28	64
8	C	4	108	1	79
	P	13	98	5	82
	B	56	117	15	89
Mean values	C	18	119	2	79
	P	26	132	8	100
	B	58	125	30	101

B = border zone; C and P = center and periphery, respectively, of ischemic zone.

demonstrate that this severe impairment in digoxin binding cannot entirely be explained by the observed alterations in regional flow after reperfusion. In all animals with 2 hours of occlusion and 15 minutes of reperfusion, regional flow was restored to values greater than those in nonischemic zones, whereas ^{3}H-digoxin uptake was substantially reduced to values ranging from 45 to 65 percent of nonischemic uptake.

Mean arterial blood pressure did not change significantly during the occlusion period in any of the three groups of animals and was not altered from control values after 15 minutes of reperfusion.

Discussion

Our study shows that coronary reperfusion instituted after 2 or 6 hours of coronary occlusion is associated with greatly reduced in vivo myocardial digoxin binding, which cannot entirely be accounted for by persistent reductions in regional blood flow during the reperfusion period. Reduced digoxin binding after reperfusion of ischemic myocardium was a graded response, in terms of both duration and severity of ischemia. Impairment of digoxin uptake was greatest in the center of the ischemic zone, which showed the greatest degree of S-T segment elevation during the occlusion period.

After 1 hour of occlusion, reperfusion resulted in almost complete recovery of digoxin uptake by myocardial tissue in ischemic and border zone regions. However, there was some possible impairment of digoxin binding in endocardial layers in the center and periphery of the ischemic zone, but the reduction (15 percent) was not statistically significant. Reperfusion after 2 hours of coronary occlusion was associated with impaired binding of the glycoside in the center and periphery of the ischemic zone, but border zone uptake was only slightly reduced. When reperfusion was carried out after 6 hours of coronary occlusion, ^{3}H-digoxin uptake in central and peripheral ischemic zones was greatly reduced and was quantitatively similar to mean values observed in animals with coronary occlusion without reperfusion.[12] Previous studies[12] in animals with 1 hour of occlusion but no reperfusion demonstrated that ^{3}H-digoxin concentration in subendocardial layers of the center of the ischemic region was reduced to 10 percent of the nonischemic control concentration. Thompson et al.[15] also found a three- to fourfold decrease in ^{3}H-digoxin concentration in experimental canine infarcts after acute coronary occlusion. Also, as previously demonstrated in nonreperfusion experiments, subendocardial concentrations of ^{3}H-digoxin were reduced significantly more than subepicardial concentrations, resulting in reversal of the normal endocardial to epicardial transmural gradients.

Mechanism of impaired digoxin binding in ischemic myocardium: The mechanism for impairment of left ventricular myocardial digoxin uptake in animals undergoing coronary occlusion undoubtedly partly reflects altered regional flow to ischemic and nonischemic tissue. Local increases in extracellular potassium concentration may also contribute to impaired digoxin binding in ischemic myocardium. It has been shown that elevated serum potassium concentrations reduces myocardial ^{3}H-digoxin binding in normal canine myocardium,[16] an effect that is probably related to the known ability of potassium to reduce the rate of cardiac glycoside binding to $(Na^+ + K^+)$-adenosine triphosphatase. The marked decrease in digoxin binding in ischemic tissue may also be related to other causes of alteration of the ability of $(Na^+ + K^+)$-adenosine triphosphatase to bind the drug, including substrate (adenosine triphosphate) limitation. Adenosine triphosphate is required for optimal binding of cardiac glycosides to isolated and partially purified $(Na^+ + K^+)$-adenosine triphosphatase.[9] It is evident that intact metabolic machinery is required for optimal binding to myocardial tissue in the models studied by Marks.[17] An additional possibility is that structural damage or loss of the enzyme complex might occur under the conditions existing in ischemic myocardium.

Reversibility of changes: The reperfusion experiments were undertaken to determine the potential reversibility of alterations in myocardial digoxin uptake observed during ischemia. Reperfusion would be expected to be effective, restoring substrate delivery and "washing out" accumulated lactic acid and potassium from previously occluded zones. However, restoration of coronary flow after 2 and 6 hours of coronary occlusion appeared to have little effect in reversing the ischemia-induced alteration in digoxin binding. In our study, reflow of blood to ischemic myocardium after 15 minutes of reperfusion was not impaired except in endocardial regions of the ischemic zone in three of the four animals with 6 hours of occlusion. In fact, regional flow to ischemic myocardium after 15 minutes of reperfusion in dogs undergoing 2 hours of coronary occlusion was greater than flow to normal myocardium because of the presence of reactive hyperemia in the region. We cannot, of course, exclude the possibility that longer periods of reperfusion might be more effective in reversing altered binding of the glycoside.

Taken together, these experiments indicate that when coronary blood flow is restored to areas of myocardium rendered acutely ischemic for more than 1 hour, myocardial tissue in the ischemic zone shows progressive diminution in binding of digoxin. These results are consistent with ischemia-induced structural or functional alteration in myocardial digitalis binding sites that may be secondary to loss of the integrity of myocardial membrane $(Na^+ + K^+)$-adenosine triphosphatase, a putative digitalis receptor.

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Echocardiographic Diagnosis of Tetralogy of Fallot

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The echocardiographic features of tetralogy of Fallot were defined in 25 patients with this malformation proved by cardiac catheterization. The echocardiographic characteristic that was present in all patients and that was most sensitive was the abrupt ending of the interventricular septal echoes with the aorta overriding the ventricular septal defect. The following additional echocardiographic features were frequently demonstrated in these 25 patients: right ventricular enlargement (20 patients), hypertrophy of the interventricular septum (20 patients), diminution of the right ventricular outflow tract (21 patients) and widening of the aorta (24 patients). The suggestion is made that the most specific echocardiographic pattern of tetralogy of Fallot is the finding of several echocardiographic abnormalities rather than the single feature of aortic overriding. Recognition of the altered anatomic relation coupled with a complete echocardiographic evaluation of all cardiac structures is a reliable means of diagnosing tetralogy of Fallot.

The early use of echocardiography was primarily concerned with the evaluation of acquired heart disease. Improvements in echocardiographic technique and equipment and an enhanced knowledge of echocardiographic anatomic features have led to a wider application of this procedure in recent years. In the field of congenital heart disease, echocardiography was first demonstrated to have diagnostic reliability in patients with an atrial septal defect.[1,2] Subsequently, there have been reports suggesting echocardiographic changes in patients with ventricular septal defect,[3] single ventricle,[3,4] double outlet right ventricle,[4] hypoplastic left heart syndrome,[4,5] hypoplastic right heart syndrome,[4,5] truncus arteriosus,[3,5,6] dextrotransposition of the great vessels[5,7] and tetralogy of Fallot.[3,5,8,9] To date, however, the sensitivity and the specificity of these findings have not been adequately evaluated in large numbers of patients with each condition. The purpose of this study was to determine whether there is a pattern of echocardiographic features characteristic of tetralogy of Fallot.

Methods

Echocardiographic evaluation was performed in 25 patients with tetralogy of Fallot proved by cardiac catheterization at either Grady Memorial Hospital or Emory University Hospital. The patients ranged in age from 3 months to 42 years; 10 were female. The majority of the echocardiograms were obtained during the patients' hospitalization for cardiac catheterization; however, a few patients who had undergone cardiac catheterization prior to this study and who had not been operated on were recalled for echocardiography.

Recordings: Echocardiograms were obtained using a Unirad C-100 series diagnostic echoscope system and either a 2.25 megahertz transducer or a 3.5 megahertz transducer with an acoustic lens collimating the sonic beam for a tissue depth of 7.5 cm. The echocardiograms were recorded on either Polaroid photographs of the oscilloscope or on strip chart film. The patients were

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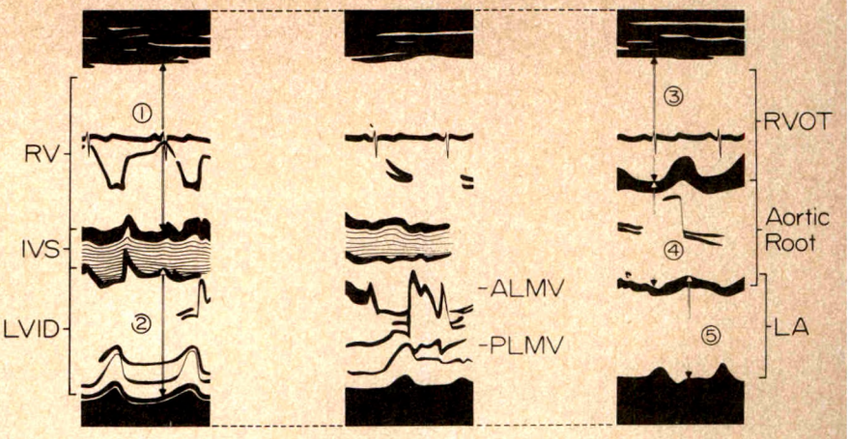

FIGURE 1. Schematic representation of a scanning recording with the transducer beam rotated from a point just distal to the mitral valve cephalad and medial to the aortic valve area. The various measurements made in each patient are indicated by the numbered dimensions. 1 = right ventricular dimension (RV). 2 = left ventricular internal dimension (LVID). 3 = right ventricular outflow tract (RVOT). 4 = aortic root dimension. 5 = left atrium (LA). ALMV = anterior leaflet of mitral valve; IVS = interventricular septum; PLMV = posterior leaflet of mitral valve. (See text.)

studied in the left lateral decubitus position with the transducer placed along the left sternal border. The transducer was positioned in the interspace that allowed optimal recordings of both leaflets of the mitral valve with the echocardiographic beam directed perpendicularly to the chest wall. This mitral position was used as the pivotal point for all subsequent recordings. From this position the transducer was angulated laterally and slightly inferiorly to obtain the right ventricular, interventricular septal and left ventricular dimensions. A "scanning" M-mode recording was made while the transducer beam was rotated from the mitral position in a slightly medial and cephalad direction to the aortic valve area. The scanning recording was made to determine if the normal relation between contiguous structures was maintained. Finally, with the transducer beam directed in a medial and cephalad direction, a recording was made for measurement of the right ventricular outflow tract and aortic and left atrial dimensions.

Measurements: Figure 1 is a schematic representation of an echocardiogram demonstrating the series of measurements made in each patient. The right ventricular dimension was the distance in millimeters from the right ventricular epicardial echo (or, if this was indistinct, from a plane 0.5 cm below the dense chest wall echoes) to the most anterior of the interventricular septal echoes. The left ventricular internal dimension was the distance measured from the most posterior interventricular septal echoes to the endocardial position of the left ventricular wall echoes.[1] These measurements were made in tracings recorded at a level immediately below the mitral valve leaflets and at the time of the peak R wave of a simultaneously recorded electrocardiogram. The right ventricular outflow tract, which is the relatively echo-free space anterior to the anterior aortic wall, was measured from the dense chest wall echoes to the most anterior echoes from the aortic root. The right ventricular outflow tract, aorta and left atrium were all measured at the level at which the aortic cusps could be visualized.

Control subjects: In addition to the 25 patients who constitute the basis of this report, 53 control subjects underwent similar measurements. These were 4 patients with truncus arteriosus, 4 patients with double outlet right ventricle and 45 normal subjects with no clinical or echocardiographic evidence of disease. The normal subjects were classified into the following groups: 10 children aged 2 days to 6 months (average 1 1/2 months) with a body surface area of less than 0.55 m^2, 10 children aged 3 to 12 years (average 5 years) with a body surface area of 0.55 to 1.0 m^2 and 25 adults aged 18 to 35 years (average 26 years).

Results

Tables I and II summarize the data from the 25 patients with tetralogy of Fallot. Table III lists the mean and range of values for our patients along with the normal range for those echocardiographic measurements that are distorted in patients with tetralogy of Fallot. In each of these tables the patients are classified into Groups A, B and C on the basis of body surface area. These particular groupings were used not because there were significant differences in our results among the three groups of patients studied but because previously defined normal dimensions were arranged according to these values for body surface area.

The five characteristic echocardiographic features of tetralogy of Fallot were found to be: (1) an increased right ventricular diameter, (2) thickening of the interventricular septum, (3) narrowing of the right ventricular outflow tract, (4) increased aortic root diameter and (5) overriding of the aorta (Fig. 2 and 3).

Right ventricular dimension: This dimension was increased in 20 of the 25 patients and the enlargement was much more impressive in adults than in children. To obtain a more accurate reflection of the relative degree of right ventricular enlargement in these patients, we calculated the ratio of right ventricular dimension to the left ventricular internal diameter (Table II). All 25 patients demonstrated a significant increase in this ratio, which has been reported to be approximately 0.33[1] and was found to be 0.33 or less in each of our normal groups. The thickness of the anterior free wall of the right ventricle could not be satisfactorily recorded in most cases; however, the interventricular septum was abnormally thickened in 20 of the 25 patients.

Right ventricular outflow tract: In contrast to the enlargement of the main right ventricular chamber, the width of the right ventricular outflow tract was decreased in 21 of the 25 patients. This decrease was well reflected by the significant reduction in the ratio of the diameter of the right ventricular outflow tract to the left atrial anteroposterior diameter.

Previous data[8] had indicated that in adults this

ratio is normally 1.5 or greater. Our series of normal subjects suggests that this ratio is 1.2 or greater for children with a body surface area of less than 0.55 m^2 and 0.9 or greater for children with a body surface area of 0.55 to 1.0 m^2.

Aortic root diameter: As expected, the aortic root was enlarged in all but 1 of the 25 patients (Case 24, 1 of the 5 adults). In contrast to the right ventricular enlargement, the aortic root enlargement appeared to become less striking with age.

Aortic overriding: The most impressive and the most characteristic echocardiographic feature in our cases of tetralogy of Fallot was aortic overriding (last column, Table I). In all 25 patients the interventricular septal echoes ended abruptly rather than blending in a normal fashion without interruption into the anterior aortic wall echoes. Thus, the anterior aortic wall echoes were located abnormally, in a plane anterior to the interventricular septal echoes, with the aorta overriding the echocardiographically defined ventricular septal defect.

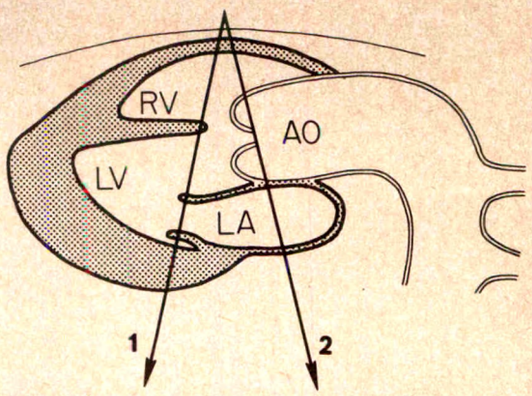

FIGURE 2. Schematic representation of cardiac anatomy in tetralogy of Fallot. As the transducer beam is directed along vector 1, echoes from the anterior right ventricular wall, interventricular septum, anterior and posterior leaflets of the mitral valve and posterior left ventricular wall are recorded. When the transducer is then rotated and the beam directed along vector 2, echoes from the anterior and posterior walls of the overriding aortic root and from the posterior left atrial wall are recorded. AO = aortic root; LA = left atrium; LV = left ventricle; RV = right ventricle.

TABLE I

Echocardiographic Measurements in 25 Patients with Tetralogy of Fallot

Case no.	Age (yr) & Sex	BSA*	LVID (mm)	RVD (mm)	IVS (mm)	Aorta (mm)	Aortic Overriding (mm)
			Group A (BSA <0.55m^2)				
1	3/12F	0.27	22	15	8	17	8
2	6/12F	0.31	22	14	7	21	10
3	16/12M	0.51	25	23	7	22	21
4	2F	0.51	20	23	7	23	20
5	2M	0.54	27	15	7	24	9
6	2M	0.51	28	16	7	23	15
7	2M	0.50	23	17	8	NM	NM
8	3F	0.54	26	15	9	25	14
Normal range[3]			13–32	3–13	4–6	7–15	0
			Group B (BSA 0.55–1.0m^2)				
9	4F	0.55	27	17	10	27	13
10	4F	0.58	30	30	7	30	15
11	4F	0.60	NM	16	6	30	20
12	4M	0.61	26	20	8	27	14
13	4M	0.62	34	16	10	30	16
14	5F	0.57	24	15	7	25	10
15	5F	0.62	32	12	7	26	6
16	6M	0.74	37	21	8	25	15
17	6F	0.76	31	19	7	27	17
18	6M	0.73	30	19	8	28	12
19	10F	0.80	35	30	11	33	23
20	10M	0.82	30	15	10	30	11
Normal range[3]			24–42	4–18	5–7	14–22	0
			Group C (BSA >1.0 m^2)				
21	27F	1.28	36†	20†	12	40†	15
22	30F	1.50	22†	24†	14	23†	23
23	30M	1.65	19†	24†	12	23†	20
24	42M	1.74	20†	17†	15	22†	25
25	30M	1.80	24†	35†	14	25†	23
Normal range[3]			19–23*	5–12*	7–11	13–22*	0

* From formula of Dubois and Dubois[9a]

† Per square meter body surface area.

BSA = body surface area; IVS = interventricular septum; LVID = left ventricular internal dimension; NM = not measurable because one of the structures necessary for the measurement was not seen in the echocardiogram; RVD = right ventricular dimension.

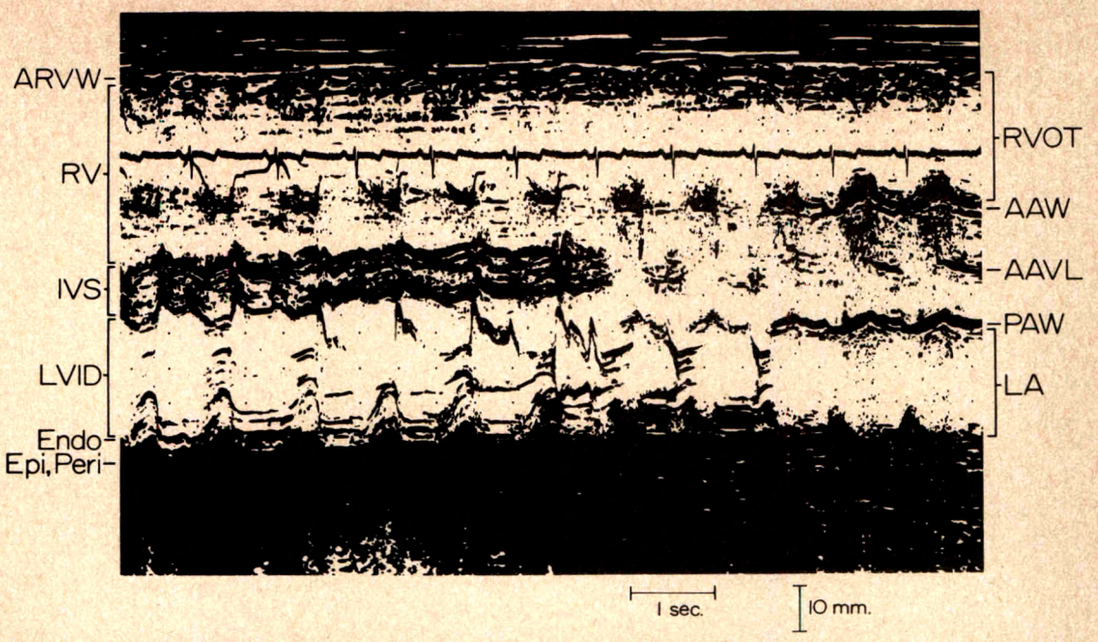

FIGURE 3. Case 22. Echocardiographic arc scan recording. The sweep begins with the transducer beam directed across the right ventricle, interventricular septum and left ventricle at the level of the chordae tendineae of the mitral valve. As the recording is made the transducer is gradually angulated in a cephalad and medial direction, first recording the motion of the mitral valve leaflets, and subsequently echoes from the right ventricular outflow tract, aorta and left atrium. AAVL = anterior aortic valve leaflet; AAW = anterior aortic wall; ARVW = anterior right ventricular wall; Endo = endocardium; Epi =epicardium; IVS = interventricular septum; LA = left atrium; LVID = left ventricular internal dimension; PAW = posterior aortic wall; Peri = pericardium; RV = right ventricle; RVOT = right ventricular outflow tract.

TABLE II

Echocardiographic Ratios and Catheterization Measurements in 25 Patients with Tetralogy of Fallot

		Echocardiographic Data		Catheterization Data	
Case no.	Age (yr) & Sex	RVD/LVID (diameter)	RVOT/LA (width)	% O_2 Sat.	RVP/ LVP*
1	1/4F	0.68	1.00	88	1
2	1/2F	0.59	1.00	92	1
3	1 1/2M	0.92	0.92	94	1
4	2F	1.15	0.80	50	<1
5	2M	0.55	0.72	91	1
6	2M	0.57	0.80	90	<1
7	2M	0.73	NM	92	1
8	3F	0.57	0.73	84	<1
9	4F	0.62	0.70	83	1
10	4F	1.0	1.00	92	1
11	4M	NM	0.55	75	>1
12	4M	0.76	0.93	80	1
13	4M	0.47	0.68	83	1
14	5F	0.63	0.75	86	>1
15	5F	0.37	1.00	93	1
16	6M	0.56	0.93	75	1
17	6F	0.61	0.71	87	1
18	6M	0.63	0.63	85	>1
19	10F	0.85	0.65	90	>1
20	10M	0.50	0.85	90	1
21	27F	0.55	0.66	78	1
22	30F	1.09	0.75	57	>1
23	30M	1.23	0.95	NA	NA
24	42M	0.85	0.85	80	<1
25	30M	1.45	1.00	85	1

* A difference of 10 mm Hg or greater in right and left ventricular peak systolic pressure was considered significant.

NA = catheterization data not available; O_2 Sat = systemic arterial oxygen saturation; RVD/LVID = ratio of right ventricular dimension to left ventricular internal dimension; RVOT/LA = ratio of right ventricular outflow tract to anteroposterior left atrium; RVP/LVP = ratio of peak right ventricular systolic pressure to peak left ventricular systolic pressure.

TABLE III

Comparative Echocardiographic Data of Patients with Tetralogy of Fallot and Normal Subjects

	Group A (BSA <0.55)	Group B (BSA 0.55–1.0)	Group C (BSA >1.0)
RV diameter (mm)			
Mean	17.3	19.2	24.0
Range	14–23	12–30	17–35
Normal range	3–13	4–18	4–13*
IVS width (mm)			
Mean	7.5	8.3	13.4
Range	7–9	6–11	12–15
Normal range	4–6	5–7	7–11
RVOT/LA			
Mean	0.85	0.78	0.84
Range	0.70–1.0	0.55–1.0	0.66–1.0
Normal range	1.2†	0.9†	⩾1.5§
AoR diameter (mm)			
Mean	22.1	28.2	26.6
Range	17–25	25–33	22–40
Normal range	7–15	14–22	13–22*
Ao overriding (mm)			
Mean	13.9	14.3	21.2
Range	8–12	6–23	15–25

* Per square meter body surface area (all other values are absolute).
† Personal observations.

Ao = aortic; AoR = aortic root; BSA = body surface area (m^2); IVS = interventricular septum; RV = right ventricular; RVOT/LA = ratio of diameter of right ventricular outflow tract to left atrial anteroposterior diameter.

Discussion

Normal subjects: In normal patients, the ratio of the echocardiographic right ventricular dimension to left ventricular diameter is no greater than 0.33, and the ratio of the diameter of the right ventricular out-

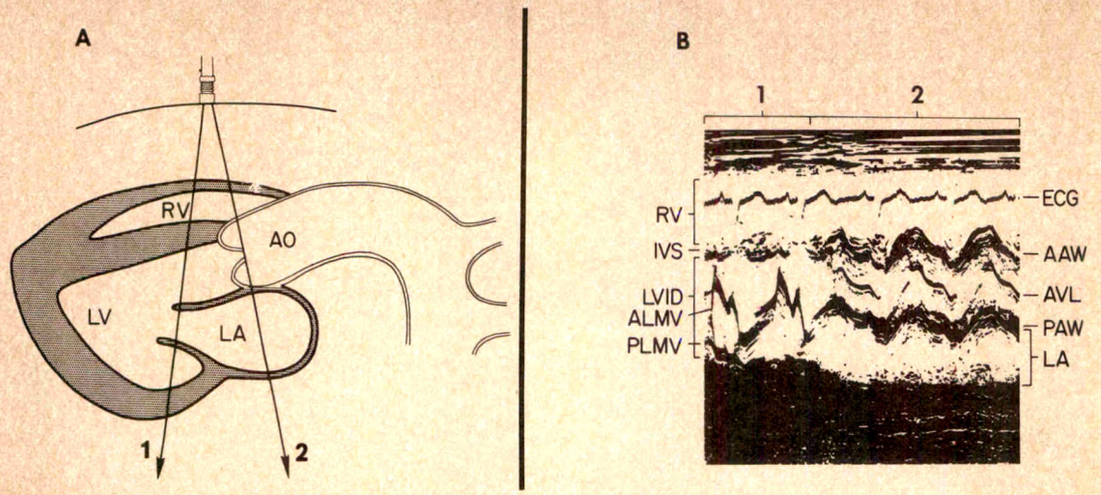

FIGURE 4. Normal cardiac anatomy, schematically presented (**A**) and as manifested in the echocardiogram of a normal subject (**B**). As the transducer beam is directed along vector 1 as demonstrated in **A**, the echoes received and recorded are those displayed under area 1 of **B**. The structures outlined with the transducer at this angulation include the right ventricle, interventricular septum, the left ventricle, the anterior and posterior leaflets of the mitral valve. The transducer is then rotated in a slightly cephalad and medial direction until the echo beam is directed along vector 2. With the beam assuming this direction the following structures (as demonstrated in area 2 of **B**) are delineated: anterior aortic wall, aortic valve leaflets, posterior aortic wall and left atrium. AAW = anterior aortic wall; ALMV = anterior leaflet of mitral valve; AVL = aortic valve leaflet, ECG = electrocardiogram; IVS = interventricular septum; LA = left atrium; LVID = left ventricular internal dimension; PAW = posterior aortic wall; PLMV = posterior leaflet of mitral valve; RV = right ventricle.

flow tract to that of the left atrium is 1.5 or greater.[1,8] In addition, a scanning echocardiographic recording demonstrates both the normal continuity of the interventricular septum with the anterior aortic wall and the normal continuity of the anterior leaflet of the mitral valve with the posterior aortic wall (Fig. 4).

Tetralogy of Fallot: In this lesion there are two major alterations in the echocardiographic features of the right ventricle. First, there is enlargement in the right ventricular chamber size, which is well reflected by an increased ratio of right ventricular dimension to left ventricular internal dimension. Second, there is a narrowing of the right ventricular outflow tract, as evidenced by a reduction of the ratio of the right ventricular outflow tract to the left atrium. This narrowing presumably reflects the infundibular stenosis seen in most, if not all, patients with tetralogy of Fallot. In addition, the interventricular septum was abnormally thickened in all but four patients. Both this change and the increase in the right ventricular diameter were most impressive in the adults. Although it has been previously suggested that the interventricular septum was primarily a left ventricular structure, subsequent studies have demonstrated that the septum may hypertrophy in cases of pulmonary hypertension and pulmonary stenosis.[10] Our study documents the thickening of the interventricular septum in association with the increased right ventricular pressure in tetralogy of Fallot. It also suggests that at least part of the increase in right ventricular dimension represents true hypertrophy of the free wall of the right ventricle, although this is difficult to determine echocardiographically. The motion of the hypertrophied interventricular septum was normal in all our cases. Others[2,3,11] have found this motion to be normal in most instances of pressure overload of the right ventricle though not in patients with volume overload of the right ventricle.

The most sensitive and characteristic echocardiographic feature in patients with tetralogy of Fallot is an abrupt ending of the interventricular septal echoes with the aorta sitting astride the septal defect. The finding was first described by Gramiak and Shah[12] in 1971 and has subsequently been demonstrated in other studies.[3,5,8,9] Although this echocardiographic feature of tetralogy of Fallot distinctly separates these patients from normal subjects, it may also be present in patients with other forms of cyanotic heart disease. Thus, our four patients with truncus arteriosus revealed aortic overriding of a high interventricular septal defect,[3,5,6] and our one patient with Taussig-Bing complex with biventricular origin of the pulmonary artery demonstrated overriding of the septum by a great vessel.[13]

Differentiation from truncus arteriosus: Truncus arteriosus is the lesion most difficult to differentiate with certainty from tetralogy of Fallot by echocardiography since patients with it may demonstrate all five echocardiographic features of tetralogy of Fallot. However, if the presence of the pulmonary valve can be demonstrated together with these features, the diagnosis of tetralogy of Fallot can be established.[6] In our patients with tetralogy of Fallot in whom a search was made for the pulmonary valve, echoes from this structure were routinely recorded. Nevertheless, the number of patients examined is too small for us to state categorically that failure to record pulmonary valve echoes reliably distinguishes

truncus arteriosus from tetralogy of Fallot. An additional feature that we have noted to favor the diagnosis of truncus arteriosus is massive aortic root dilatation. All four of our patients with truncus arteriosus demonstrated an aortic root diameter of 40 mm or more whereas that of the largest aortic root found in a patient with tetralogy of Fallot of a comparable age group has been 25 mm.

Differentiation from Taussig-Bing complex: Our one case of Taussig-Bing complex was differentiated from tetralogy of Fallot by echocardiography on the basis of a normal right ventricular diameter plus mitral-semilunar valve discontinuity. Although Gramiak et al.[14] reported that the anterior leaflet of the mitral valve and the posterior aortic root wall were normally at the same depth in the echocardiogram, our study suggests that these structures are not always at exactly the same depth. In 25 patients with no clinical evidence of heart disease and with a normal left ventricular diameter by echocardiogram, the difference in depth of the anterior leaflet of the mitral valve and the posterior aortic root wall at the beginning of ventricular systole ranged from 0 to 8 mm. In 11 patients the depth of these two structures was identical; in 2 patients the depth of the structures varied by 1 mm, in 2 by 2 mm, in 6 by 3 mm, in 2 by 5 mm and in 2 by 8 mm. This finding partly represents an echocardiographic distortion due to the alignment of the transducer beam and the structures in question; nevertheless, arc scanning recordings from multiple positions frequently demonstrated these structures to be at slightly different levels. Consequently, we have required a difference of more than 10 mm in levels of the anterior leaflet of the mitral valve and the posterior aortic wall for the definite diagnosis of mitral-semilunar valve discontinuity. In our four cases with mitral-semilunar valve discontinuity and in four of five patients in the study of Chesler et al.[13] the difference in levels is more than 10 mm. Recently, Chung et al.[8] indicated that 7 of their 17 patients with tetralogy of Fallot had a difference of 5 to 22 mm in level of anterior leaflet of the mitral valve and the posterior aortic root wall. By our range of normal variation, at least some of their patients would have echocardiographic confirmation of the expected anatomic arrangement.

Differentiation from dextrotransposition of the great vessels: The other major form of cyanotic heart disease requiring separation from tetralogy of Fallot is dextrotransposition of the great vessels. The expected distinguishing echocardiographic feature would be the aortic overriding. As others have previously demonstrated echocardiographically, the aorta in cases of dextrotransposition lies immediately below the chest wall echoes and anterior to the pulmonary artery.[5,7] In cases of transposition neither of the origins of the great vessels should be astride the interventricular septal echoes.

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Congenital and Surgical Atrioventricular Block Within the His Bundle

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In three patients with congenital heart disease the site of atrioventricular (A-V) block was localized within the His bundle with the aid of His bundle electrograms. In one patient with first degree A-V block and normal QRS configuration, electrophysiologic studies revealed "split" His potentials. The other two patients had complete A-V block, and their His bundle electrograms revealed His spikes both proximal and distal to the site of block. One of the two patients, who had a pattern of left bundle branch block in the electrocardiogram, had surgically induced complete A-V block after repair of an ostium primum atrial septal defect. The other patient with congenital A-V block had a narrow QRS complex and, in addition to complete block within the His bundle, prolonged A-V nodal conduction time but no associated cardiac anomaly. Both patients with complete heart block required pacemaker insertion.

The natural history of intra-His bundle block is not known, and it is difficult to recommend appropriate therapy. More electrophysiologic studies are needed in patients with A-V block to determine the prognostic significance of such block or conduction delay in the His bundle.

His bundle recordings have demonstrated[1–3] that the sites of delay or block along the specialized conducting tissues between the sino-atrial node and the ventricles may involve one or more of the following locations: the atria, atrioventricular (A-V) node, bundle of His, right or left bundle branch and the Purkinje network. The standard electrocardiogram sometimes fails to localize precisely the site of delay or block.[1–9] Block in the His bundle has no representation in the surface electrocardiogram but has been deduced by clinical electrocardiographers.[6] Narula et al.[2] first documented block within the His bundle. They termed their findings "split" H potentials and suggested that one of these (H_1) was recorded proximal to and the other (H_2) distal to an area of block. Others[2–4,8–17] have reported similar observations (Table I).

This report deals with three patients with delay or block within the His bundle documented by His bundle recordings. The report (1) presents the first documented instance of surgically induced block within the His bundle, (2) demonstrates the second instance of congenital heart block within the His bundle with no associated cardiac anomaly, (3) documents two additional instances of congenital heart block occurring within the His bundle, and (4) tabulates the previous 20 reported cases of intra-His bundle block.

Methods

His bundle electrograms were obtained in three children with congenital heart disease during the course of a prospective study of patients with conduction disturbances. The His bundle electrograms were obtained using conventional techniques.[18–20] The patient and all electrical equipment were securely grounded. Bipolar and tripolar electrode catheters were used with in-

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TABLE I

Reported Cases of Block Within the His Bundle

Study	Case no.	Age (yr) & Sex	Type of Block	QRS Complex		Cause	Associated Lesions	H_2-V (msec)
				Configuration	Duration (sec)			
Narula et al.[2-4]	1	84M	Mobitz I (3:2)	Normal	0.08	...	...	40
Narula et al.[2-4]	2	...	Mobitz II (2:1)	Normal	0.06	...	...	70
Narula et al.[2-4]	3	48F	Complete	Normal	0.08	...	...	40
Rosen et al.[9]	4	70M	2:1	Normal	...	ASHD	...	60
Rosen et al.[10]*	5	...	Mobitz II	...	...	ASHD	...	...
Rosen et al.[11]	6	17F	Complete	Normal	0.06	Congenital	None	35
Rosen et al.[12]	7	23M	Complete	RBBB	0.14	Penetrating trauma	VSD	40
Schuilenburg & Durrer[13]	8	71F	Mobitz II	Normal	0.09	ASHD	...	50
Schuilenburg & Durrer[13]	9	27M	2:1	RBBB	0.13	ASHD	...	30
Schuilenburg & Durrer[13]	10	78M	Complete	Normal	0.09	ASHD	...	45
Schuilenburg & Durrer[13]	11	82M	Complete	RBBB	0.12	ASHD	...	45
Gupta el al.[14]*	12	...	Mobitz II	...	...	...	...	...
Gupta et al.[14]*	13	...	Mobitz II	...	...	...	...	...
Gupta et al.[14]	14	74F	Complete	Normal	0.06	...	...	40
Gupta et al.[15]	15	87M	Complete	Normal	0.06	...	...	40
Gupta et al.[15]	16	85M	Complete	RBBB	0.11	...	...	45
Jacobson & Scheinman[16]	17	81M	Mobitz II	LBBB	0.13	Catheter-induced	...	60
Jacobson & Scheinman[16]	18	56M	Mobitz II	LBBB	0.17	Catheter-induced	...	61
Bharati et al.[17]	19	67M	1° A-V	RBBB	0.12	Calcific and degenerative	...	48
Bharati et al.[17]	20	85F	Complete	LBBB, RBBB	...	Calcific and degenerative	...	48
Present report	21	2M	1° A-V	Normal	0.08	Congenital	DORV	34
Present report	22	20F	Complete	LBBB	0.12	Surgical	1° ASD	35
Present report	23	9F	Complete	Normal	0.08	Congenital	None	45

* Data obtained from abstract only rather than full paper.
ASD = atrial septal defect; ASHD = arteriosclerotic heart disease; A-V = atrioventricular; DORV = double outlet right ventricle; LBBB = left bundle branch block; RBBB = right bundle branch block; VSD = ventricular septal defect.

terelectrode distances of 1 or 10 mm, or both. All records were obtained on a multichannel oscilloscopic photographic recorder (Electronics for Medicine DR-8) at paper speeds of 100 to 200 mm/sec with filter frequencies of 0.1 to 200 hertz for electrocardiographic leads and 40 to 500 hertz for electrographic recording.

Several potentials were recorded sequentially in the interval from the low right atrium to ventricle (LRA-V), but the potential after the low right atrial (LRA) deflection that was farthest from the ventricular electrogram was designated the H potential. The potential between the H and V potentials is the right bundle (Rb) potential. The interval from the low right atrium to the His bundle potential (LRA-H) was measured from the onset of the low right atrial depolarization to the onset of the first rapid deflection of the His bundle potential. The interval from the His bundle to the ventricle (H-V) was measured from the first rapid deflection of the His bundle potential to the earliest ventricular activity in either surface or intracardiac recordings. The interval from the right bundle to the ventricle (Rb-V) was measured from the initial rapid deflection of the first potential after the His deflection to the earliest ventricular activity. When split His bundle potentials were recorded with intact A-V conduction, measurements were made of the LRA-H_1, H_1-H_2 and H_2-V intervals. When complete block occurred between H_1 and H_2, only the LRA-H_1 and H_2-V intervals were measured. All intervals were measured in milliseconds. The normal values for intervals from our laboratories[20] are as follows: LRA-H interval 60 to 129 msec, H-V interval 30 to 55 msec, Rb-V interval 15 to 25 msec.

Clinical Cases and Results

Case 1: The patient was a 2 year old boy with the diagnosis of double outlet right ventricle, infundibular pulmonary stenosis and persistent left superior vena cava draining into the coronary sinus. The electrocardiogram demonstrated sinus rhythm at a rate of 100/min with a prolonged P-R interval of 0.20 second (Fig. 1). First degree A-V block was evident in the initial electrocardiogram obtained at age 2 months. The QRS complexes were narrow and 0.08 second in duration. Right axis deviation and right ventricular hypertrophy were evident.

His bundle electrograms were recorded during right heart catheterization. With the tripolar catheter positioned at the tricuspid valve, two high frequency electrograms were recorded between the atrial and ventricular electrograms (Fig. 2), possibly representing "split" H potentials as defined by Narula et al.[2] Each atrial depolarization was followed by a biphasic proximal His bundle potential (H_1) at an LRA-H_1 interval of 76 seconds. The H_1–H_2 interval measured 49 msec and the H_2-V interval 34 msec. In addition, every ventricular depolarization was pre-

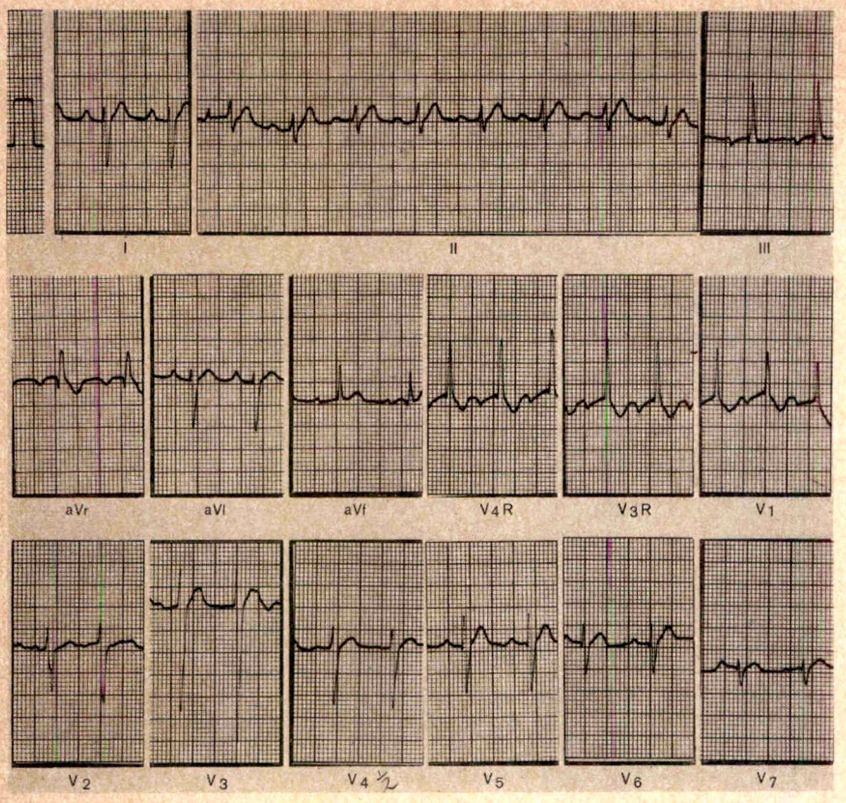

FIGURE 1. Case 1. Electrocardiogram reveals sinus rhythm, first degree A-V block, right axis deviation and right ventricular hypertrophy. The QRS complex is narrow and measures 0.08 second.

ceded by a separate biphasic spike between H_2 and V, which probably represented the right bundle branch (Rb) potential at an Rb-V interval of 16 msec.

Case 2: The patient was a 20 year old woman with a history of syncopal attacks of 2 weeks' duration and a pulse rate of 34/min. She had surgically induced complete heart block of 13 years' duration with repair of an ostium primum atrial septal defect at age 6 years. The electrocardiogram (Fig. 3) revealed a complete A-V block with an atrial rate of 62 and a ventricular rate of 34/min. There was a left bundle branch block configuration with a QRS duration of 0.12 second. The ventricular escape focus may have originated in the right bundle branch system, producing the left bundle branch block configuration.

Recording of the His bundle electrogram showed that every atrial depolarization was followed 100 msec later by a His potential (H_1) and that every escape ventricular complex was preceded by 35 msec by a second His potential (H_2) (Fig. 4). In addition, a second smaller deflection (Rb) preceded the ventricular complex between H_2 and V at an Rb-V interval

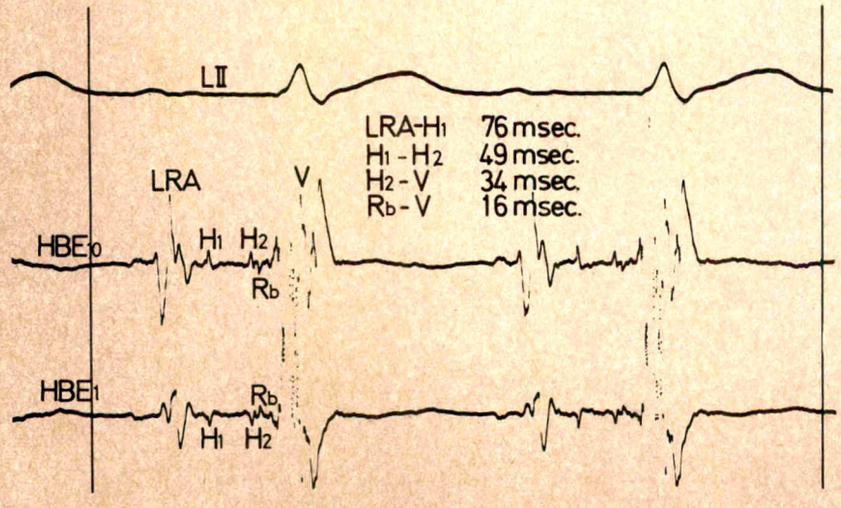

FIGURE 2. Case 1. Representative strip of His bundle electrogram (HBE). **From top to bottom:** electrocardiographic lead II, and His bundle electrograms with respective interelectrode distances of 10 and 1 mm. Paper speed is 200 mm/sec, time lines are at 1,000 msec intervals. Sinus rhythm is evident at a cycle length of 600 msec. Each atrial beat is followed 76 msec later by a His potential (H_1). This potential is followed at 49 msec later by a second potential (H_2) that precedes a ventricular complex with a constant interval of 34 msec. The right bundle branch potential (Rb) recorded simultaneously precedes the QRS complex at an Rb-V interval of 16 msec. HBE = His bundle electrocardiograms. LRA = low right atrium.

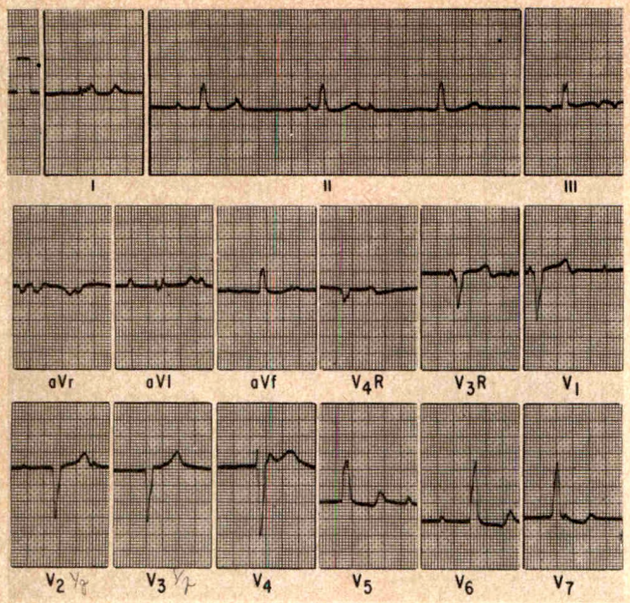

FIGURE 3. Case 2. Electrocardiogram reveals complete A-V block. The escape rhythm is characterized by a left bundle branch block pattern with a QRS duration of 0.12 second.

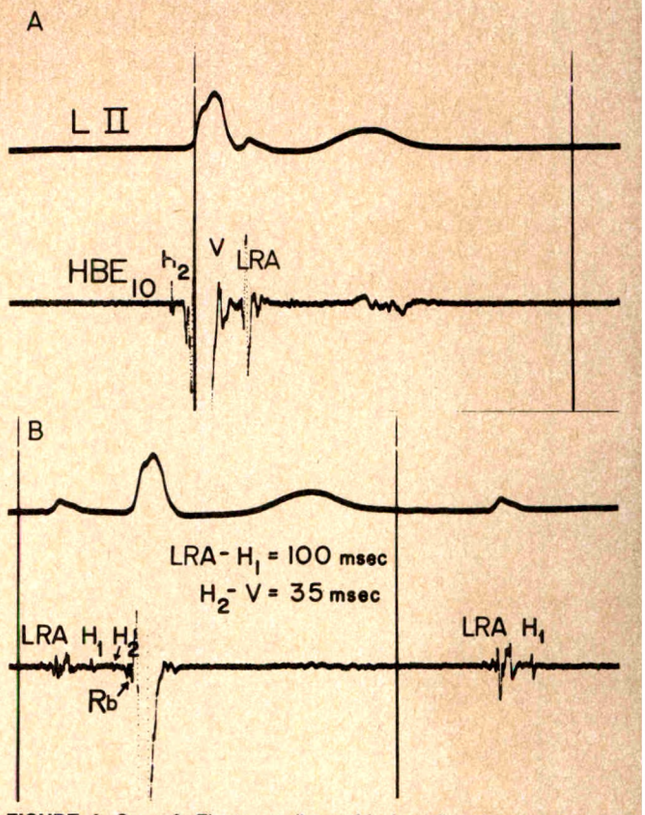

FIGURE 4. Case 2. Electrocardiographic lead II and representative strips (**A** and **B**) from the His bundle electrogram. Complete A-V block is evident with an atrial rate of 62 and a ventricular rate of 41/min. Each low right atrial (LRA) potential in **B** is followed by a high frequency potential (H_1). Each QRS complex is preceded by a high frequency potential (H_2) recorded from the His bundle catheter as well as an Rb potential preceding the ventricular complex. Time lines are at 1 second intervals; paper speed is 200 mm/sec.

of 20 msec. Atrial pacing had no effect on the ventricular rate. Intravenous administration of 0.5 mg of atropine sulfate increased the atrial rate from 61 to 100/min and the ventricular rate from 41 to 50/min. A permanent pacemaker was later inserted.

Case 3: The patient was a 9 year old girl with congenital complete heart block first noted at age 8 months. The electrocardiogram revealed complete A-V block with an atrial rate of 100 and a ventricular rate of 32/min. The QRS complex had a normal configuration and a duration of 0.08 second (Fig. 5). With exercise, the atrial rate increased to 150 and the ventricular rate to 50/min. Hemodynamic and angiographic studies of the right and left sides of the heart revealed no abnormalities. There were no signs suggesting corrected transposition of the great vessels.

His bundle electrograms revealed that every atrial depolarization was followed 220 msec later by a His bundle potential (H_1) and that every ventricular escape complex was preceded by 45 msec by a second deflection (Fig. 6). In addition, a third deflection (Rb) preceded the ventricular complex at an Rb-V interval of 19 msec.

Right atrial pacing was carried out at rates of 120 to 190/min. As the atrial rate was increased, the LRA-H_1 interval was prolonged with 1:1 conduction being maintained to H_1 up to a paced rate of 190/min. Intravenous administration of atropine sulfate (0.3 mg) increased the atrial rate from 100 to 139/min and the ventricular rate from 32 to 50/min. A permanent pacemaker was inserted, primarily because of the patient's slow heart rate, premature ventricular contractions and poor exercise response.

Discussion

Electrophysiology: Electrophysiologic studies suggested that our patients had His bundle disease, with H_1 being recorded proximal to and H_2 distal to an area of conduction delay in the His bundle. In Case 1,

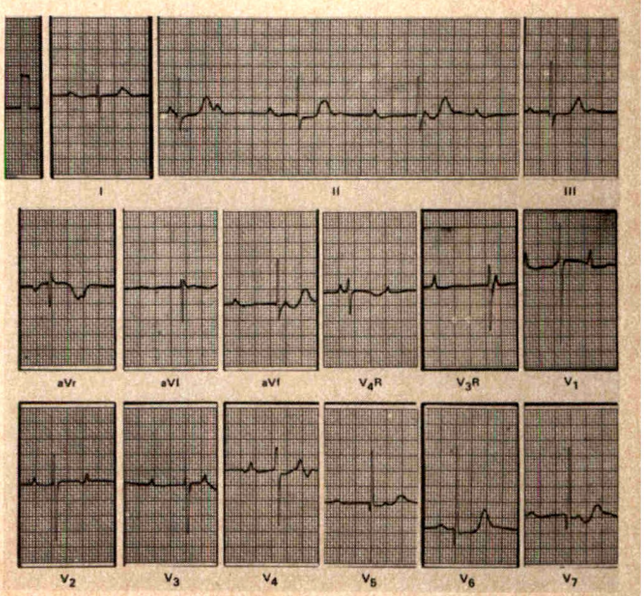

FIGURE 5. Case 3. Electrocardiogram reveals complete A-V block. The escape rhythm at a rate of 32/min is characterized by a normal QRS configuration with a duration of 0.08 second.

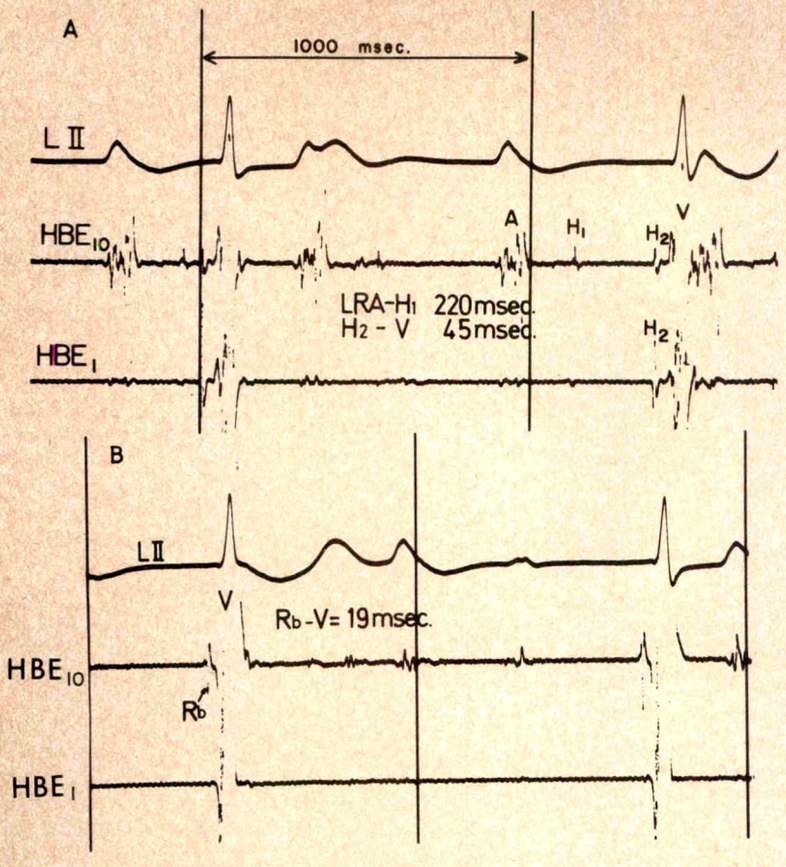

FIGURE 6. Case 3. Lead II of the electrocardiogram and His bundle electrograms. Complete A-V block is evident with an atrial rate of 100 and a ventricular rate of 32/min. **A,** two bundle of His deflections (H_1 and H_2) are recorded. The LRA-H_1 interval is prolonged. **B,** note the right bundle potential preceding the QRS complex recorded with the catheter advanced farther into the ventricle.

if one accepts H_1 as a His bundle potential, then H_2 is presumably a His bundle potential recorded distal to H_1 or a right bundle branch electrogram. The catheter electrode was presumed to be in the usual position for recording the His potential since both atrial and ventricular electrograms were identifiable at the same position in which the H_1 and H_2 potentials were recorded. In addition, each QRS complex was preceded by another potential, probably a right bundle branch (Rb) potential occurring 18 msec after H_2 and 16 msec before the QRS complex.

In Case 2, the pattern of splitting was somewhat different from that of Case 1. The most likely explanation is that a proximal His potential (H_1) followed every low right atrial deflection and was not conducted to the ventricles. The distal H_2 potential was seen preceding escape beats with a left bundle branch block pattern. The H_2-V interval was normal. The subsidiary pacemaker probably arose in the bundle of His just proximal to its bifurcation but distal to the focal block. The QRS configuration in the surface electrocardiogram of the resulting ventricular beats indicated an additional impairment of impulse conduction to or in the left bundle branch. One might anticipate a prolonged H-V interval in the presence of left bundle branch block. In keeping with this possibility, the H_2 potential in this case may have originated from the proximal right bundle branch, in which case one could postulate surgical injury to the distal bundle of His or to the most proximal portion of both main divisions, with a right bundle branch impulse origin. However, a normal H-V interval as in this case has been reported in the presence of left bundle branch block.[21–23] In addition, a right bundle branch (Rb) potential was recorded between the H_2 and V potentials. It is sometimes not possible to record clear H_1, H_2 and Rb potentials simultaneously, as in this case and those reported by Schuilenburg and Durrer.[24] We did not succeed in localizing the site of origin of the H_2 deflection by stimulating the heart by way of the His bundle recording electrodes because the ventricles were always activated immediately on stimulation. We believe that the His bundle lesion producing A-V block in this patient was related to surgical trauma. The likelihood of a traumatic lesion involving the proximal left bundle branch is obvious. This case is the first known instance in which His bundle recording identified the site of surgical A-V block within the bundle of His.

Case 3 is unique in several aspects. It is the second reported case of congenital A-V block with no associated anomaly in which intra-His bundle block was documented by His bundle electrogram (Table I). In addition, the findings represent an exception to the general rule relating the level of block to the configuration of the QRS complex. Each of the nonconducted atrial impulses is followed by a His deflection. The complete block is not within the A-V node although

the LRA-H_1 interval is prolonged. The QRS complexes are normal and are preceded by a single His deflection with a normal H_2-V interval. The findings are compatible with intra-His bundle block in which the pacemaker for the ventricles resides within the bundle of His but below the level of block.

Diagnosis of intra-His bundle block: Block within the His bundle cannot be distinguished by surface electrocardiograms from block within the A-V node.[15] In either instance, if the block is complete, the QRS configuration is of a supraventricular type, unless an associated bundle branch block is present.[13] Functional properties of the escape rhythms may be of some value in determining their site of origin. It is possible that the association of the slow ventricular rate with a narrow QRS complex indicates block within the His bundle. Unlike patients with A-V nodal block, patients with intra-His bundle block have no or only a small increment in ventricular rate after intravenous administration of atropine.[2–4,13] This is possibly because of the lack of parasympathetic control of a more distal His bundle pacemaker. However, the ventricular rate increased slightly after atropine in our Cases 2 and 3 and in two patients with intra-His bundle block described by Gupta et al.[15] The response of the subnodal A-V conduction to cholinergic stimulation is still controversial and needs to be resolved.

Two patterns of "splitting" are described in this report, one occurring with intact conduction (Case 1) and the other occurring with complete A-V block (Cases 2 and 3). In Cases 1 and 3 the splitting was presumably due to focal lesions in the His bundle. Pathologic correlation is not available but the patients are presumed to have developmental disruptive lesions in the His bundle.

Etiology: The origin of complete heart block in the His bundle has been attributed to traumatic causes,[12] coronary occlusion,[10] calcific and degenerative lesions,[17] postsurgical status (Case 2) and congenital lesions (Cases 1 and 3).[11] Congenital A-V block maybe an isolated abnormality of the conduction system as in our Case 3 or may be associated with other congenital cardiac malformations. Pathologic findings noted in reviews of congenital A-V block by Lev[25] and Carter et al.[26] include imperfect formation of, or lack of, the His bundle, and inflammatory or noninflammatory degeneration of the bundle, possibly resulting from an intrauterine inflammatory process. Carter et al.[26] reviewed the histologic features of 28 reported cases and provided an anatomic classification of congenital lesions of the cardiac conduction system.

Incidence: Intra-His bundle blocks have been described infrequently in English language reports. In contrast, French investigators reported a 20 percent incidence rate of intra-His bundle lesions in patients after acute myocardial infarction.[27] Guerot et al.[28] reported that in 11 (18 percent) of 60 cases of chronic A-V block the site of block was localized within the His bundle by His bundle electrograms. A similar incidence rate (19 percent) was reported by Puech et al.[29]

Life history: Very little is known about the clinical evolution of lesions within the His bundle in man. El-Sherif et al.[30] provided an experimental validation of the pathophysiologic findings after ligation of the anterior septal artery in dogs. They demonstrated that the evolution of His bundle block is a progressive phenomenon, and that Mobitz II block represents the initial stage of failure of impulse propagation in intra-His bundle lesions. The duration of block in our Cases 2 and 3 was 13 and 8 years, respectively.

It has previously been shown[31] that the site of block resides in the A-V node in patients with congenital A-V block with narrow QRS complexes. In our Cases 1 and 3, as well as in a case of congenital A-V block described by Rosen et al.,[11] the site of congenital block was demonstrated to be within the His bundle by His bundle electrograms. In our Case 3, the prolonged LRA-H_1 interval indicated an additional conduction abnormality in the A-V node. It is evident from the reported cases (Table I) that intra-His bundle conduction delay or block could simulate types I, II, III and high degree A-V block. By surface electrocardiogram the diagnosis of block within the His bundle cannot be made with certainty particularly when mixed conduction lesions exist. Block within the His bundle is more common than reported and, furthermore, His bundle recording in children with A-V block is of value to localize precisely the site of delay or block. It is anticipated that this technique may be of value in assessing the clinical evolution and pathophysiology of intra-His bundle lesions, their prognosis and the need for prophylactic pacemaker therapy.

Acknowledgment

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Long-Term Follow-Up of Two Infants with an Implanted Cardiac Pacemaker

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The clinical course of two patients with congenital heart block who had pacemaker implantation at age 7 and 8 months, respectively, is reviewed. One patient at age 10 years has had nine pulse generators inserted; the other has had six implantations, the most recent a lithium iodine pacemaker, during 8 1/2 years of observation. Both patients have shown normal physical development and emotional maturation despite multiple hospitalizations and pacemaker replacements, thus demonstrating that electrical pacing, initiated in infancy, can be maintained through childhood without adverse effects.

Electrical pacing of the heart has been utilized over the past decade for the management of symptomatic atrioventricular (A-V) block in young infants.[1–4] However, because experience has been limited and no published information is available as to long-term survival and follow-up, questions as to growth, development and psychological adjustments have remained unanswered.

This communication reviews the clinical course of two children with complete heart block who had pacemaker implantation at 7 and 8 months of age, respectively. They have been under our care since birth, and their growth and developmental pattern for more than 8 years of close follow-up study is presented. The original indication for permanent pacing in Case 1 was intractable congestive heart failure associated with a congenital cardiac malformation.[5,6] The second patient required pacemaker implantation because of episodes of Stokes-Adams syncope with ventricular tachyarrhythmia.[7]

Case Reports

Case 1

This 10 year old girl was born in September 1964 in a full-term spontaneous delivery. Weight was 3,375 g and length 50 cm. She was the first of two children born to a 17 year old Caucasian mother (height 160 cm) and 26 year old father of West Indian origin (height 168 cm).

Bradycardia was noted in utero for 2 days before delivery. After birth, A-V conduction was variable and included periods of normal sinus rhythm and second degree A-V block. Complete heart block at a ventricular rate of 44/min became established at age 3 months. Cardiovascular study revealed congenitally corrected transposition of the great vessels with a large ventricular septal defect and pulmonary hypertension. Because of unremitting congestive heart failure, pulmonary arterial banding was performed at age 4 months and myocardial wires were inserted for cardiac pacing. The infant's heart was continuously paced for the next 3 months until it was clearly established that a minimal ventricular rate of 90/min was required to maintain cardiac compensation and permit a satisfactory feeding pattern consistent with adequate weight gain. An atrial synchronous pacemaker (Cordis Atricor Junior) was implanted in the left side of the abdomen at age 7 months with transthoracic insertion of atrial and ventricular epicardial leads (Fig. 1).

During the ensuing 9 years, the child had nine hospital admissions for pac-

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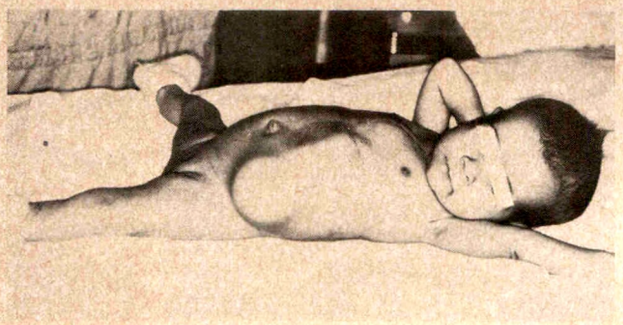

FIGURE 1 (left). Patient 1 at age 7 months after initial implantation of pacemaker (Cordis Atricor). Reprinted from Harris et al.[5] by permission of CV Mosby.

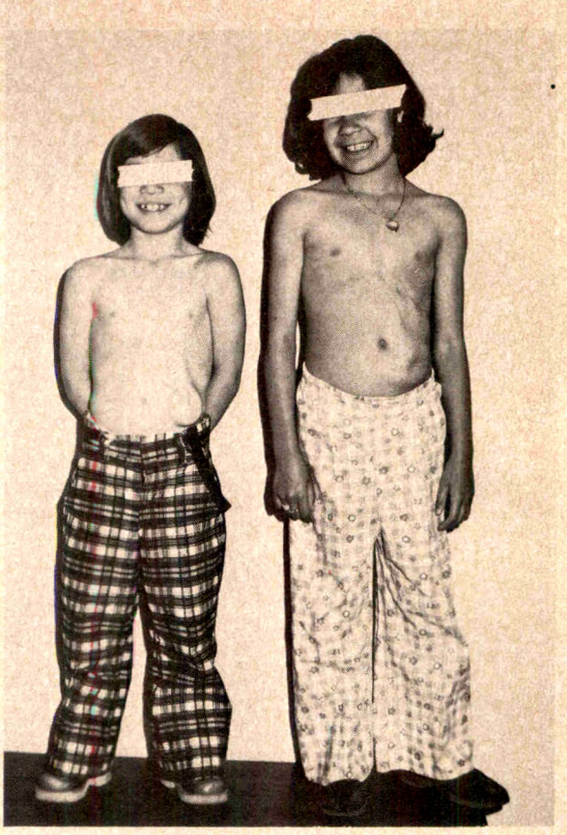

FIGURE 3 (right). Patient 1 **(right)** at age 9 3/4 years with ninth pulse generator (Medtronic Chardack) and Patient 2 **(left)** at age 8 years with fifth implanted pulse generator (Cordis Ventricor).

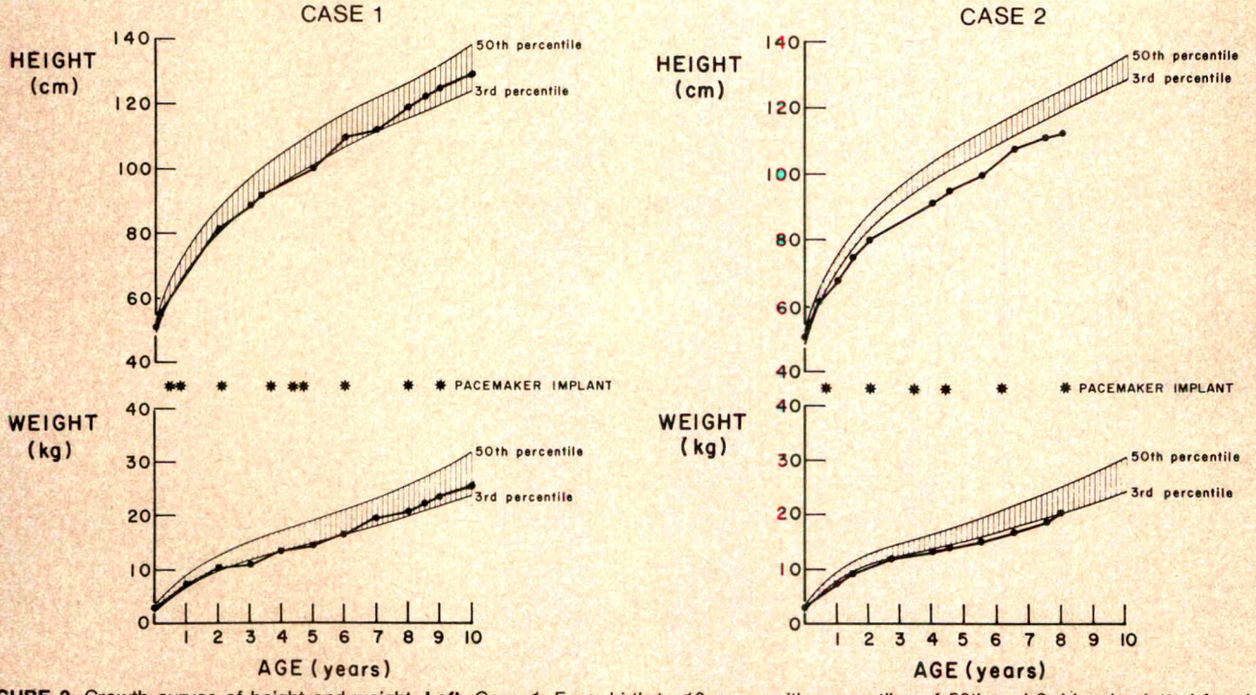

FIGURE 2. Growth curves of height and weight. **Left,** Case 1. From birth to 10 years with percentiles of 50th and 3rd levels plotted for girls. **Right,** Case 2. From birth to age 8 1/2 years with percentiles of 50th and 3rd levels plotted for boys. Ages at pacemaker replacement indicated by asterisk (*). Adapted from anthropometric charts, The Children's Medical Center, Boston, Mass.: Percentile charts for measurements of girls and boys (H Stuart and associates, Department of Maternal and Child Health, Boston, Mass.) reproduced by Mead Johnson Laboratories.

ing dysfunction 3 weeks to 23 months apart (Fig. 2). The pulse generator required replacement eight times for battery depletion. The first three units were atrial synchronous and the subsequent six were asynchronous with a fixed ventricular rate. The third synchronous pulse generator was replaced at age 3 1/2 years with a fixed rate ventricular model (No. 4, Cordis Ventricor) at a rate of 90/min. The pacing rate was lowered to 70 to 82/min with successive replacements by a variety of fixed rate pulse generators (No. 5 and 6, Ventricor; No. 7, Medtronic Chardack; No. 8, Biotronik; and No. 9, Medtronic Chardack). The last unit was implanted at age 9 years with a rate of 82/min (Fig. 3).

The clinical course after the pulmonary arterial banding and pacemaker implantation was excellent. The left to right shunt was limited and a minimal right to left shunt developed with clinical findings simulating mild tetralogy of Fallot. Surgical repair of the underlying malformation is contemplated within the next few years.

Growth pattern: Measurements of weight and height (Fig. 2) indicate parallel growth curves at approximately the 3rd percentile during early childhood. By age 8 years, the curve for height rose toward the 10th percentile. These data reflect a satisfactory growth pattern in this girl with significant congenital heart disease.

Development: The child attends a regular 5th grade class at public school and is performing well. Unrestricted activity including bicycle riding and swimming has always been permitted. She appears emotionally undisturbed by pacemaker-dependency and the need for frequent operative procedures. The family has not taken an overprotective attitude toward this girl, a factor that seems to have had a positive effect on her psychological development.

Case 2

This 8 1/2 year old boy was born in May 1966 in a full-term spontaneous delivery. Weight was 2,720 g and length 50 cm. His 26 year old mother has asthma and received antihistamine and bronchodilator therapy intermittently throughout pregnancy. The boy was the second of three children born to Hispanic parents (maternal height 145 cm, paternal height 153 cm).

Bradycardia was noted for 7 weeks before delivery. At birth, the heart rate was 46 beats/min; examination was otherwise normal. The electrocardiogram indicated complete A-V block with a junctional pacemaker and rare ectopic ventricular beats. An angiocardiogram on the 2nd day of life showed normal cardiac anatomy. The infant, followed up on an outpatient basis, had ventricular rates of 42 and 52/min. Although weight gain was slow, he was asymptomatic until age 7 1/2 months. At that time otitis media and fever of 40°C developed, and he was hospitalized.

On the day after admission he had three brief generalized seizures. An electrocardiogram recorded during one of these episodes documented ventricular tachyarrhythmia. Because of these presumed Stokes-Adams attacks and electrocardiographic findings, an atrial synchronous pacemaker (Cordis Atricor) was implanted. He had a total of four hospitalizations for pacing dysfunction at intervals of 11 to 22 months during the 7 1/2 years after the initial pacemaker implantation (Fig. 3). In each instance pacemaker failure was due to pulse generator depletion; three failures occurred with the atrial synchronous models and one with the asynchronous fixed rate unit (Cordis Ventricor) which was first implanted at age 4 1/2 years.

The patient was admitted in July 1974 after 23 months of regular pacing performance with his fifth unit (also Cordis Ventricor) for elective replacement with a lithium iodine-powered generator (unipolar demand model no. 301 UD, Cardiac Pacemakers Inc.). The rate was set at 82/min. Satisfactory pacing has continued, and the patient's general health has remained excellent.

Growth pattern: Measurements of weight (Fig. 2) indicate steady growth at the 3rd percentile. Measurements of height show a descent below the 3rd percentile beginning at age 2 years, but continued growth at the same level until age 8 1/2 years. The stature of this child (Fig. 3) is proportional to that of his mother and not significantly different from that of his two siblings.

Development: This boy has always been observed to play vigorously. He attends a regular 3rd grade class without restrictions in activity. As in Case 1, the child seems to have an emotional affect appropriate for his age and does not appear to be preoccupied with the routine surrounding his pacemaker-dependency.

Discussion

Since 1964 only one other infant at our institution has had electrical pacing initiated for congenital A-V block. This patient, now nearly 2 years of age, required pacemaker implantation at age 1 month. Nine children have undergone pacemaker insertion for postsurgical block; the follow-up period in this group, which includes eight survivors, ranges from 6 months to 11 years.

The longest interval between mandatory pulse generator replacement in the two cases reported here was 23 months. In both children, generator failure always preceded elective replacement until the most recent implantation of a lithium pacemaker in Case 2. The girl (Case 1) at age 10 years has had nine electronic pulse generators inserted and the boy (Case 2) at age 8 1/2 years has had six implants. The length and positioning of the coiled lead wires from the epicardium to the left lower quadrant of the abdomen remained adequate over the years of rapid growth. Neither patient has had infection as a complication of pacemaker implantation. We anticipate that as increased longevity and safety of newer pacemaker units (such as the lithium iodine and nuclear-powered pulse generators) permit further clinical application in children, the problem of frequent hospitalizations for pacemaker replacement will be obviated.

Both children have shown steady weight gain along the curve of the 3rd percentile. The observation that the boy is short, being below the 3rd percentile for height at age 8 1/2 years, is in accord with parental stature and racial background. The girl, at age 10 years, is at the 10th percentile for height, which is also consistent with parental habitus.

Although our patients have appeared remarkably stable emotionally, potential anxiety and stress may be provoked as a result of the child's awareness of the prosthesis protruding in the abdomen, his concerns about pacemaker failure and the need for multiple hospitalizations. It is primarily due to the excellence of maternal handling and attitude that these children have adapted so well to school activities and daily

life. Psychological support of the patients and their families by the attending staff is also an important aspect of comprehensive care of pacemaker-dependent children.

Our two patients have demonstrated normal physical growth and emotional development during the 8 to 9 years after cardiac pacemaker implantation in infancy for complete heart block. Artificial pacing not only prevented potentially fatal cardiac complications but also enabled these patients to enjoy a normal childhood. Numerous infants at many medical centers have undergone pacemaker implantations with the expectation that normal growth and development will ensue. It is encouraging to note from the cases documented here that, even when multiple surgical procedures are required, pacemaker therapy initiated in infancy can be maintained in childhood without adverse effects.

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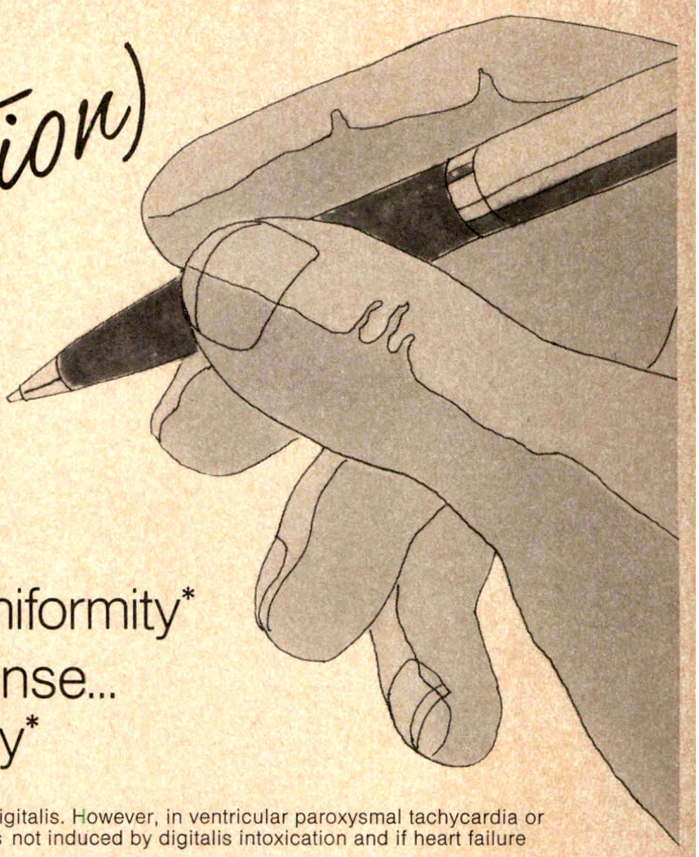

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Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used *only* in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

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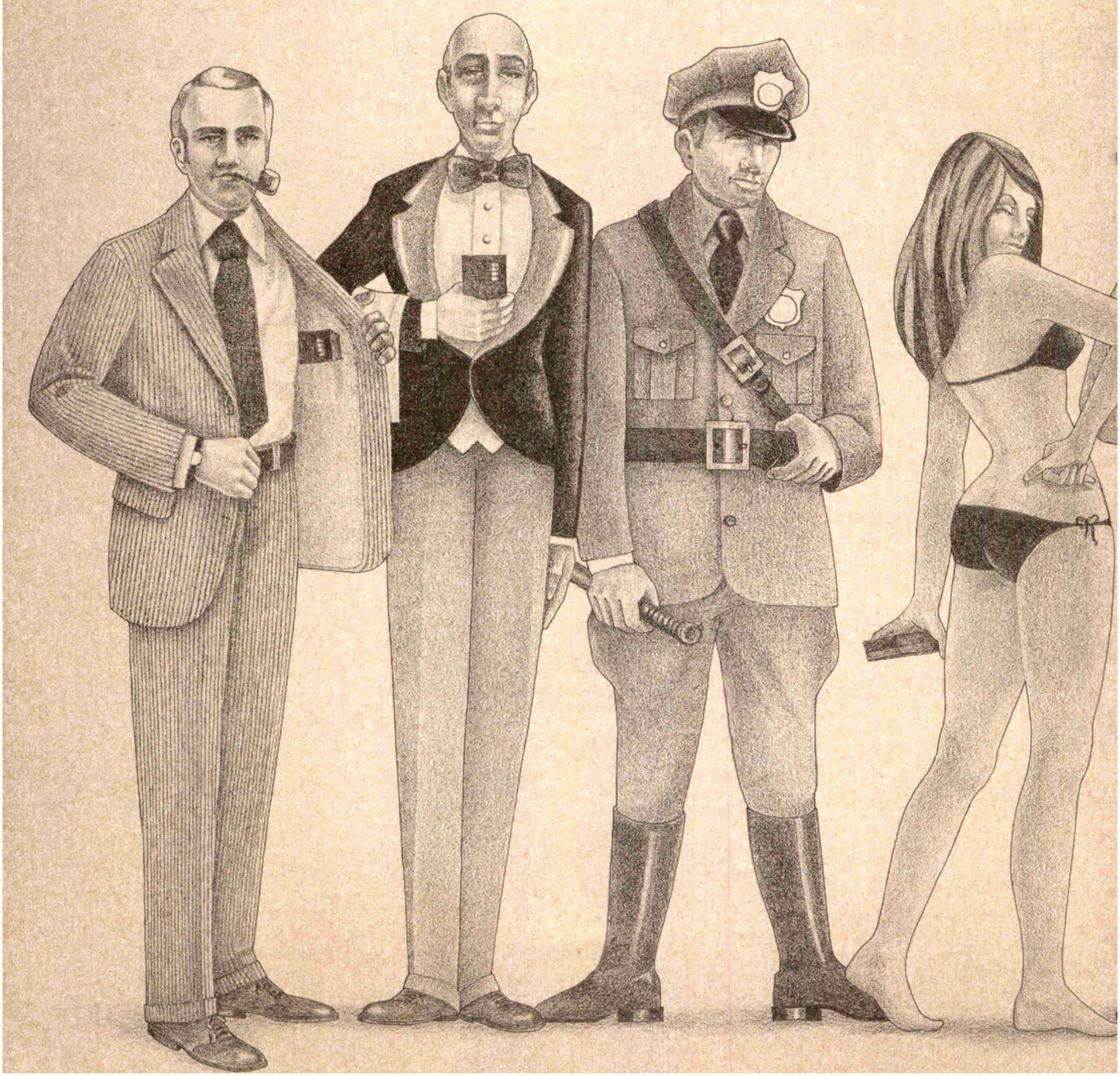

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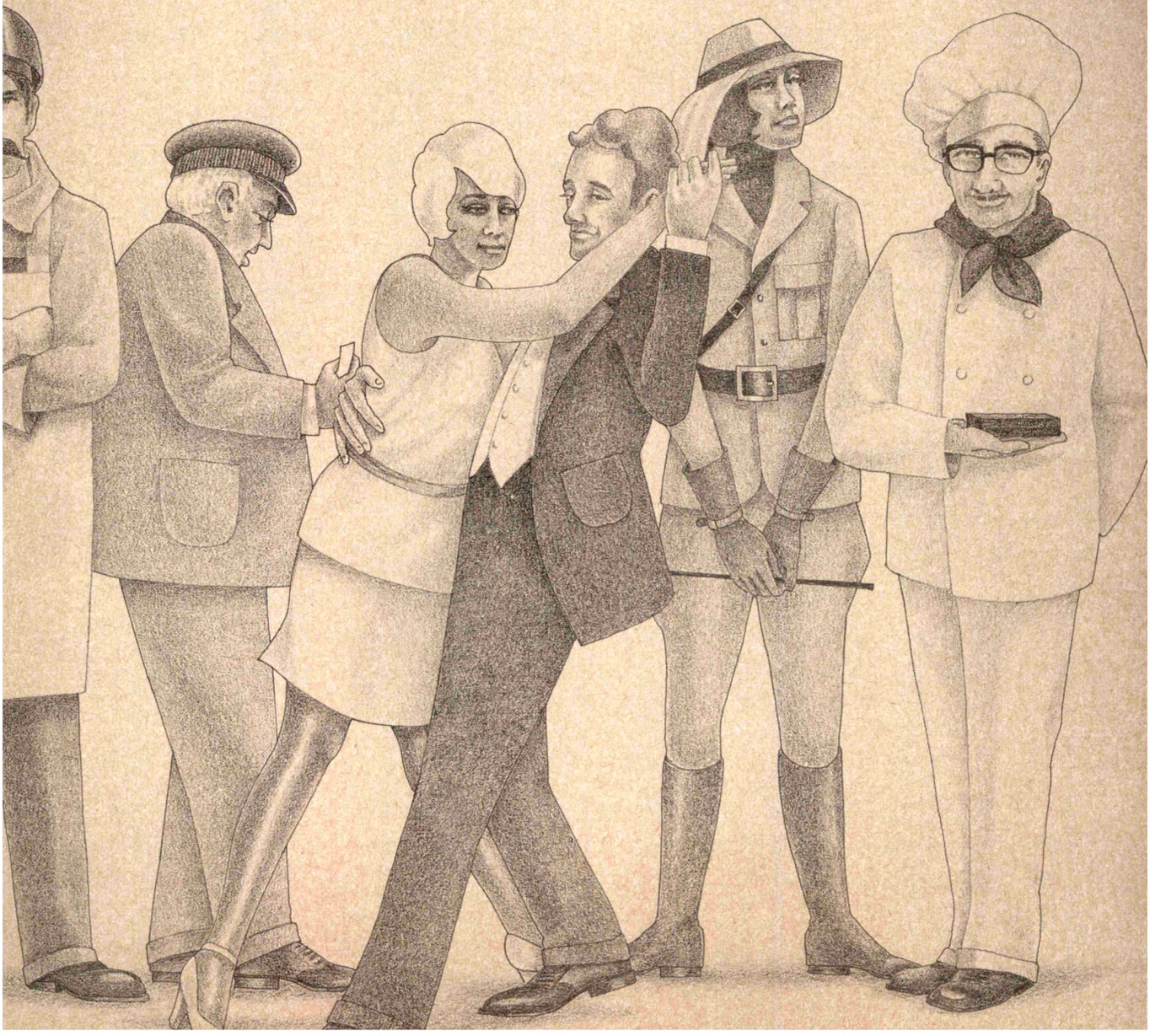

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Valium can calm the cardiac patient and help reduce his psychic tension to appropriate levels. Valium is used with most classes of primary medications such as cardiac glycosides, diuretics, vasodilators, anticoagulants, anticholinergics and antacids. Careful consideration should be given to the pharmacology of agents used with Valium, particularly those which may potentiate its action.

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The cardiac patient should know that he can generally expect Valium to help relax and calm him so that he won't feel so overwhelmed by his tension and anxiety. An explanation of the importance of the dosage regimen you prescribe may go a long way to ensure his cooperation. As with all CNS-acting agents, the patient taking Valium should be cautioned against driving or operating dangerous machinery.

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Prompt and Effective Response Valium acts promptly to help relieve psychic tension in the cardiac patient.

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Predictable Pharmacokinetically Pharmacokinetic studies of Valium demonstrate a highly predictable pattern of absorption, distribution, metabolism and excretion.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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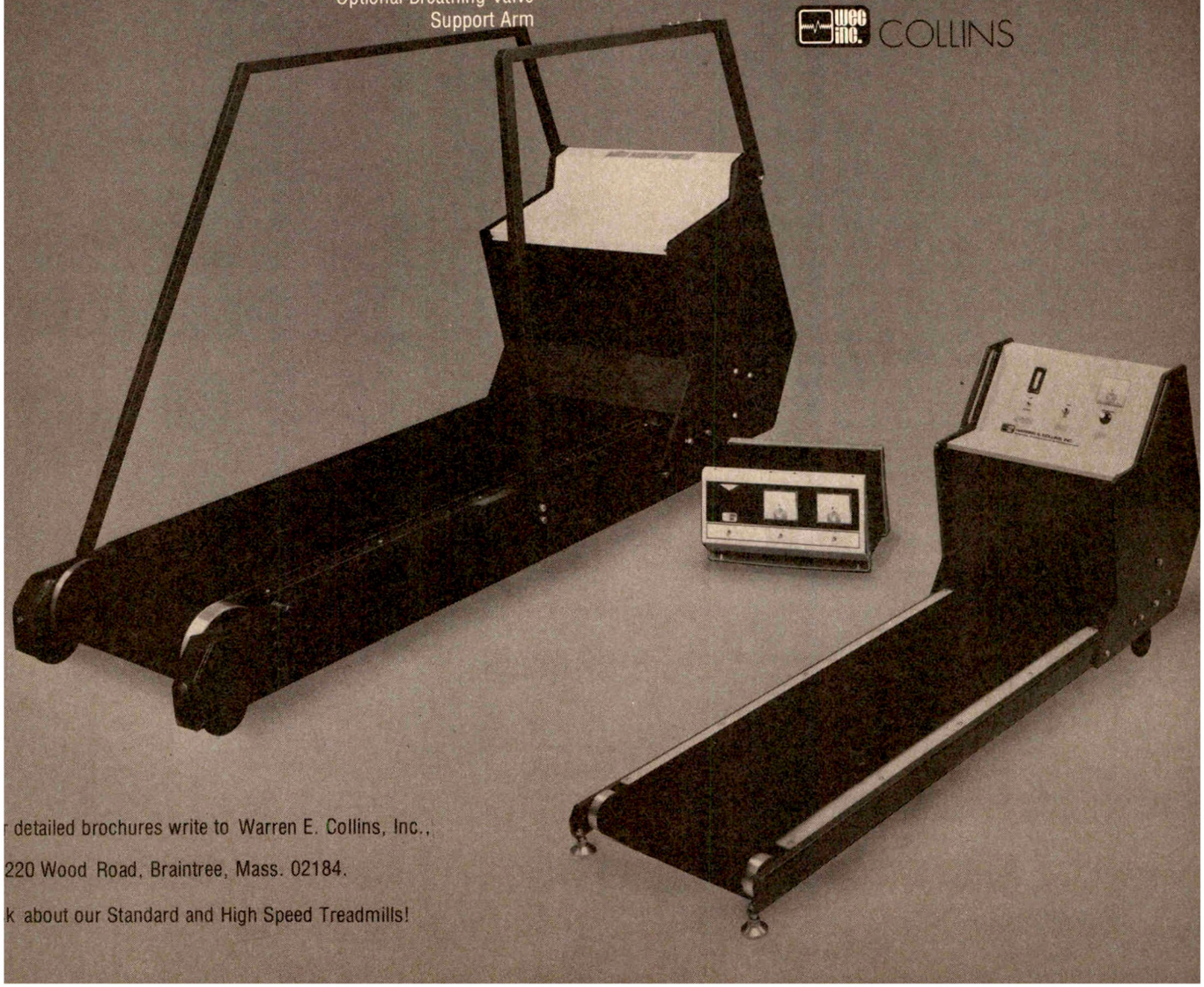

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CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps and hyperkalemia.

PRECAUTIONS: Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is often not known. Excessive or even therapeutic doses may result in potassium intoxication. The patient should be checked frequently and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.

ADVERSE REACTIONS: Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias, and heart block. When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.

DOSAGE AND ADMINISTRATION: One tablespoonful of 15 ml. (equal to 20 milliequivalents) diluted in a 4 ounce glass of water, tomato or orange juice twice daily after meals will be sufficient to replete potassium losses in most hypokalemia patients. Some patients (approximately 30 percent), will require a dose of 15 ml. t.i.d. to reverse diuretic-induced hypokalemia patients. However, these patients require close supervision to avoid the possibility of potassium intoxication. Patients should be cautioned to follow directions implicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury.

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"Potassium chloride is preferred to other salts of potassium since, in most hypokalemic states, hypochloremia is also present and chloride ion is needed to allow complete potassium replacement."[1]

decnavda yldon os raf suht evah ereh.

Thguof oho yeht hcihc krow edosinif nu eht ot ereh detacided eb. Ot rehtar gnivil os rof si ti, ereh did ydeht taw tegrof reven nac it tub, ereh yas ew tahw rebmember gnol ron, eton elttits dlrow eht tcarted.

Ro dda ot rewop roop ruo veoba raf, ti detarcesnoc evah ereh delggurth. Dna gnivil nem evarb eht dnuard sint wollah tonnac, ew etarcesnoc tonnac ew esren regral a ni tub od lduohs ew taht reporp dna.

Gnittif rehtegotla is iti evil thgim noitta taht sevil richt evag ereh ohow esoht fo ecalp-gnitser lanif a sa, dleif taht fo noitropet a etacided ot. Kom evah raw taht fo dleifelttab taerg a no tem eca ew, erudne gnol a nac det-acided os ena deviesnoc. Brosba os noitan yna ro taht rehtehw gnitset dregn.

Ereh oho esoht fo ecalp-gnitser lanif a sa, dlief taht fo noitrop a et acided pot emohic evah. Irudne gonl nac detacided os dna devi-

"In general, the chloride salt is preferable because of the participation of chloride in the renal conservation of potassium."[2]

loser ylhgir eb noitaved fo erusaem lluf tasl eht evag yeht hcihw orf esuac taht eht ot eesaercni akas ew daed deronoh eseht.

Morf that su erofed gniniamer kast taerg eht ot detacided ertew eb ot su orf rehtar si

Lauqe detaerc era nem lla taht noit isoprop eht ot detacided nda ytrebil ew deviecnoc, noitan wen a thenitnoc no htruofthgourb srehtaf ruo oga. Sraey neves dna erocsruof, htrar eet morf hsire ton llahs elps eht rof, elpoep eht yb, elpoep et fo tnemnrevog taht dna-modeerf fo htrib wen ewah llahs rednu-noitan taht niav.

Ni deid evah ton llahs daed eseht taht ev-loser ylhgir eb noitaved fo erusaem lluf tasl eht evag yeht hcihw orf esuac taht ot eesa-ereni ekas ew daed deronoh eseht.

Morf that su erofed gniniamer kast taerg eht ot detacided ertew eb ot su orf rehtar si to decnavda yldon os raf suht evah ereh.

Thguof oho yeht hcihc krow edosinif nu eht ot ereh detacided eb. Ot rehtar gnivil os rof si ti, ereh did ydeht taw tegrof reven nac it tub, ereh yas ew tahw rebmember gnol ron, eton elttits dlrow eht tcarted.

Ni deid evah ton llahs daed eseht taht ev-loser ylhgir eb noitaved fo erusaem lluf tasl eht evag yeht hcihw orf esuac taht eht ot eesa-etarcesnoc tonnac ew esren regral a ni tub od lduohs ew taht reporp dna.

Ni deid evah ton llahs daed eseht taht ev-loser ylhgir eb noitaved fo erusaem lluf tasl eht evag yeht hcihw orf esuac taht eht ot of etacided ot. Kom evah raw taht fo dleifeltnab eht yb, elpoep et fo tnemnrevog taht dna-modeerf fo htrib wen ewah llahs rednu-noitan taht niav.

Ereh oho esoht fo ecalp-gnitser lanif a sa, dlief taht fo noitrop a et acided pot emohic evah. Irudne gonl nac detacided os dna devi-ecnoc os noitan yna ro noitan taht rehte gnit-set raw, livic taerg a ni degagne era ew won.

Lauqe detaerc era nem lla taht noit isoprop eht ot detacided nda ytrebil ew deviecnoc, noitan wen a thenitnoc no htruofthgourb srehtaf ruo oga. Sraey neves dna erocsruof, htrar eet morf hsire ton llahs elps eht rof, elpoep that niav.

Ni deid evah ton llahs daed [illegible]
loser ylhgir eb noitaved [illegible] erusaem lluf tasl
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eesaercni akas ew [illegible] deronoh eseht.

Morf that su [illegible] gniniamer kast taerg
eht ot detacided [illegible] ew eb ot su orf rehtar si
to decnavda yldon [illegible] os raf suht [illegible]

Thguof oho yeh[illegible]
ot ereh detacided
si ti, ereh did yde
tub, ereh yas ew t

Lauqe detaerc era nem lla taht noit isoprop eht ot detacided nda ytrebil ew deviecnoc, noitan wen a thenitnoc no htruofthgourb srehtaf ruo oga. Sraey neves dna erocsruof, htrar eet morf hsire ton llahs elps eht rof, elpoep eht yb, elpoep et fo tnemnrevog taht dna-modeerf fo htrib wen ewah llahs rednu-noitan taht niav.

Ni deid evah ton llahs daed eseht taht ev-loser ylhgir eb noitaved fo erusaem lluf tasl eht evag yeht hcihw orf esuac taht ot eesa-ereni ekas ew daed deronoh eseht.

Morf that su erofed gniniamer kast taerg eht ot detacided ertew eb ot su orf rehtar si to decnavda yldon os raf suht evah ereh.

Thguof oho yeht hcihc krow edosinif nu eht ot ereh detacided eb. Ot rehtar gnivil os rof si ti, ereh did ydeht taw tegrof reven nac it tub, ereh yas ew tahw rebmember gnol ron, eton elttits dlrow eht tcarted.

Ro dda ot rewop roop ruo veoba raf, ti detarcesnoc evah ereh delggurth. Dna gnivil nem evarb eht dnuard sint wollah tonnac, ew etarcesnoc tonnac ew esren regral a ni tub od lduohs ew taht reporp dna.

Gnittif rehtegotla is iti evil thgim noitta taht sevil richt evag ereh ohow esoht fo ecalp-gnitser lanif a sa, dleif taht fo noitropet a etacided ot. Kom evah raw taht fo dleifelttab taerg a no tem eca ew, erudne gnol a nac det-acided os ena deviesnoc. Brosba os noitan yna ro taht rehtehw gnitset dregn.

Ereh oho esoht fo ecalp-gnitser lanif a sa, dlief taht fo noitrop a et acided pot emohic evah. Irudne gonl nac detacided os dna devi-ecnoc os noitan yna ro noitan taht rehte gnit-set raw, livic taerg a ni degagne era ew won.

Lauqe detaerc era nem lla taht noit isoprop eht ot detacided nda ytrebil ew deviecnoc, noitan wen a thenitnoc no htruofthgourb srehtaf ruo oga. Sraey neves dna erocsruof, htrar et morf fo htrib wen ewah llahs rednu--noitan [illegible]

[illegible] ton llahs daed eseht taht ev-
loser ylhgir [illegible] yed fo erusaem lluf tasl
eht evag yeht [illegible] rf esuac taht eht ot
eesaercni akas ew [illegible] ronoh eseht.

Morf that su erofed [illegible] niamer kast taerg
eht ot detacided ertew eb [illegible] t su orf rehtar si
to decnavda yldon [illegible] os raf suh[illegible] ht evah ereh.

[illegible] ow edosinif nu eht
[illegible] htar gnivil os rof
[illegible] grof reven nac it
[illegible] member gnol ron,
eton elttits dlrow eht tcarted.

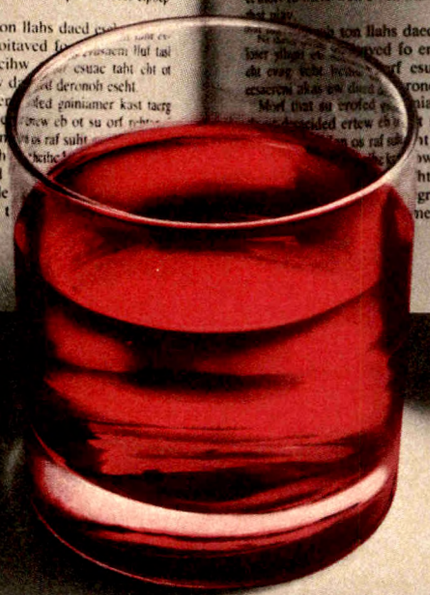
"If potassium depletion is accompanied by a deficit of chloride, it may be quite difficult to correct that deficit and dissipate the alkalosis unless adequate quantities of chloride are made available."[3]

Ereh oho esoht fo ecalp-gnitser lanif a sa, dlief taht fo noitrop a et acided pot emohic evah. Irudne gonl nac detacided os dna devi-ecnoc os noitan yna ro noitan taht rehte gnit-set raw, livic taerg a ni degagne era ew won.

Lauqe detaerc era nem lla taht noit isoprop eht ot detacided nda ytrebil ew deviecnoc, noitan wen a thenitnoc no htruofthgourb srehtaf ruo oga. Sraey neves dna erocsruof, htrar et morf fo htrib wen ewah llahs rednu--noitan that niav.

Ni deid evah ton llahs daed eseht taht ev-loser ylhgir eb noitaved fo erusaem lluf tasl eht evag yeht hcihw orf esuac taht eht ot eesaercni akas ew daed deronoh eseht.

Morf that su erofed gniniamer kast taerg eht ot detacided ertew eb ot su orf rehtar si to decnavda yldon os raf suht evah ereh.



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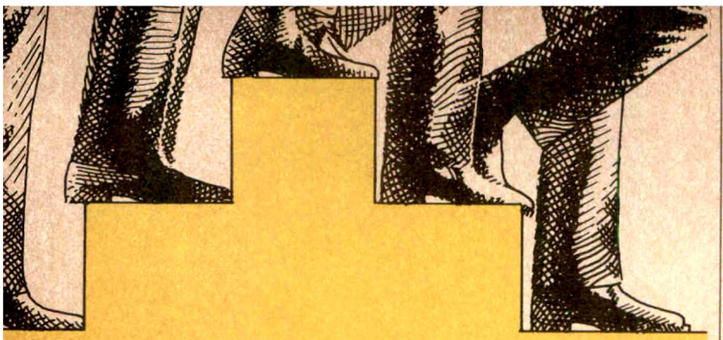

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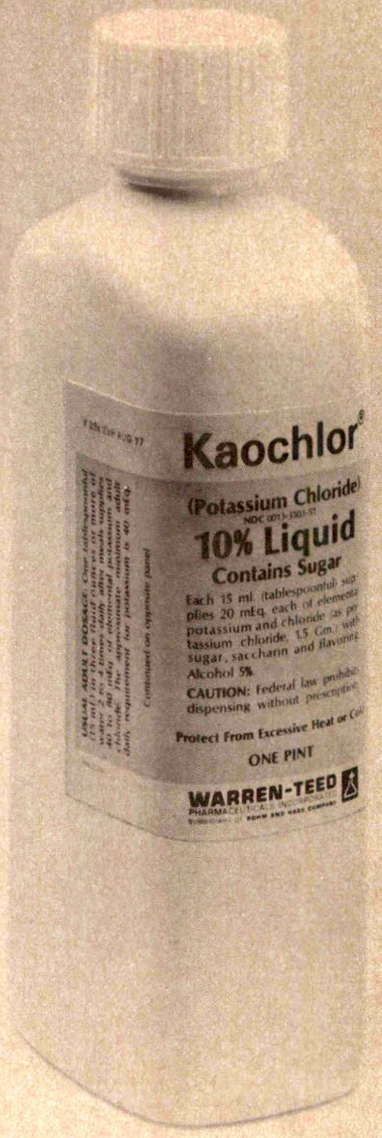

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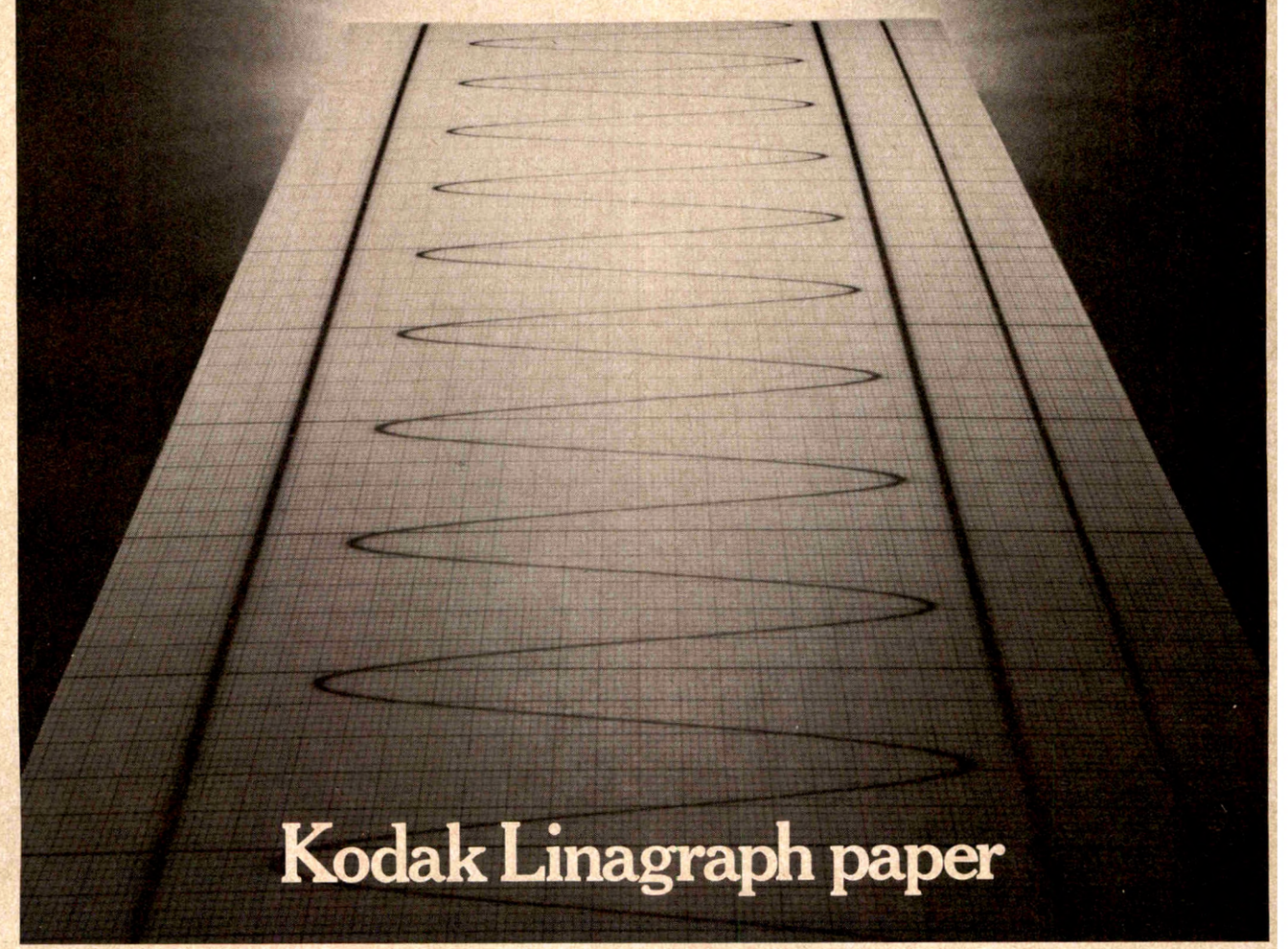

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Handy Heart Sound Simulator

J. NATHANIEL SANDERSON, MD

Washington, D.C.

A simple bedside technique of heart sound simulation using hand and stethoscope is described. The technique utilizes tissue vibration and sound conduction with the usual air column of a stethoscope to reproduce auscultatory events accurately without the distortion that often accompanies electrical production of heart sounds.

With increasing awareness of the significance of auscultatory cardiac findings, medical educators have utilized various techniques and apparatus to reproduce and simulate heart sounds. These have ranged from verbal imitation to expensive electronic heart sound simulators. In addition, libraries of heart sound recordings have been developed in some centers. Although not inordinately cumbersome, the electronic apparatus do not always readily lend themselves to instantaneous and impromptu bedside teaching. Smaller pocket-sized cassette recording devices provide a source for instant and repeated replay of observed physical findings, but are limited to records of the sounds of an individual patient or those in a library of recorded sounds. The following simple technique can be utilized to expand the availability of heart sound simulators and meet the needs of a greater number of medical educators and students.

Technique

The basic technique involves grasping the stethoscopic chest piece with the diaphragm against the palm (Fig. 1). Simple heart sounds can then be reproduced by tapping the back of the forearm or hand holding the chest piece with the opposite index finger (Fig. 2). The frequency and intensity of the sound are dependent upon the area tapped (distance up the forearm) and the vigor of the tap. Crisper, more intense sounds are created by tapping the back of the hand. Softer, lower frequency sounds are created by taps over the forearm. The simulation of first heart sounds (S_1), second sounds (S_2), physiologic third heart sounds or ventricular diastolic gallops (S_3), atrial diastolic gallops (S_4), opening snaps (OS), ejections sounds and systolic clicks is dependent upon selection of the proper frequency and timing.

Triple rhythms: The triple rhythm of a ventricular diastolic gallop is produced by rhythmically tapping the wrist and mid and proximal forearm (Fig. 2). The distance between the areas tapped helps to establish the timing intervals. In close intervals, as in the splitting of the second heart sound, it may be necessary to use the middle and index fingers of the tapping hand sequentially as in thumbing the fingers on a desk (Fig. 3). This can easily be expanded to the triple sound of the aortic and pulmonary components of the second heart sound and opening snap by adding the ring finger (Fig. 4). The rhythm of an atrial diastolic gallop (S_4) is simulated in a similar fashion but in reverse order (Fig. 5).

Murmurs: Murmurs are produced by rubbing the back of the hand in various ways depending upon the type of murmur desired. The murmur of mitral regurgitation can be simulated by tapping with the middle finger, then lightly dragging it across the back of the hand and terminating the murmur with the second heart sound by tapping with the index finger (Fig. 6). If less than a holosystolic murmur is desired, the whole sequence should be performed by the index finger since lifting the finger to tap for the second sound

From the Division of Cardiology, Department of Medicine, Georgetown University Hospital, Washington, D.C. This study was supported in part by the Benjamin May Memorial Fund, Metropolitan Heart Guild, Washington, D.C. and grants from the U.S. Public Health Service, Bethesda, Md. The paper was submitted while the author was on active duty in the U.S. Air Force as a Fellow in Cardiovascular Diseases at Georgetown University Hospital, Washington, D.C. Manuscript accepted April 23, 1975.

Address for reprints: J. Nathaniel Sanderson, MD, MAJ USAF MC, Division of Cardiology, David Grant Medical Center, Travis Air Force Base, Calif. 94535.

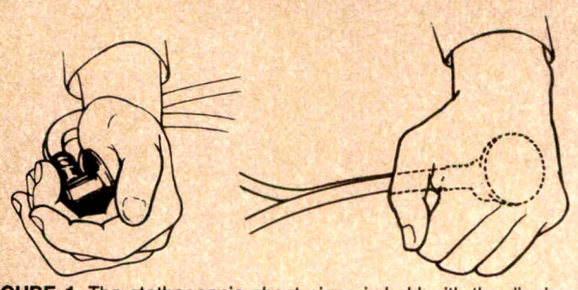


FIGURE 1. The stethoscopic chest piece is held with the diaphragm against the palm.

terminates the murmur (bottom, Fig. 6). A late systolic murmur can be produced by lifting the tapping finger after the first heart sound, before the onset of the murmur.

The harsh systolic murmur of aortic stenosis is simulated in a different fashion. The thumb of the opposite hand is pressed firmly against the back of the hand holding the chest piece to ensure increased friction. The thumb is then pushed for approximately 2.5 to 5 cm depending upon the duration of the murmur desired (Fig. 7). The addition of a diastolic blowing murmur can be achieved by softly dragging the thumb with less friction back to the original position. The change in direction of the motion of the thumb often produces a skin "pop" that conveniently simulates the second heart sound (bottom, Fig. 7). A continuous murmur is simulated by rubbing the back of the hand in a circular motion (Fig. 8). The crescendo effect is created by heavy and light pressure during alternate halves of the circle.

The simulation of the rumble of mitral stenosis requires removal of the chest piece from the closed hand. The diaphragm is placed on the thenar eminence at the base of the thumb. With the chest piece in this position, the thumb is flexed, producing a muscle tremor that simulates the rumble (Fig. 9). The addition of the first and second heart sounds and the opening snap preceding the rumble requires that the chest piece be placed on a stable surface, bell down, or held by an observer to free the tapping finger of the opposite hand. The thenar eminence is placed on the diaphragm. The thumb is flexed as described after the production of the first and second heart sounds and opening snap. For the more nimble-fingered, a systolic murmur can also be added. The rhythm of atrial fibrillation can easily be simulated by changes in the cycle intervals.

Friction rubs: Pericardial friction rubs are produced by scratching the back of the hand with the index fingernail in a rhythmic fashion to create the characteristic of three components. The presystolic or atrial component is closely followed by a louder ventricular systolic component and then the ventricular diastolic component to produce a 1, 2–3 rhythm. The leathery sound of a pleural friction rub can be produced by pinching the distal index finger and thumb of the fisted empty hand together, pushing the thumb up the distal phalanx. The sound is transmitted to the closed hand holding the chest piece by simply touching the hands together (Fig. 10). The reproducibility of these sounds varies with the oil and moisture of the hands since a fair amount of friction is required. Often placing an index card between the index finger and thumb while performing the same maneuver will provide the desired effect.

The unique sound of mediastinal emphysema can be produced by touching the diaphragm to the cupped palm of the left hand. The diaphragm will stick to the palm. As the diaphragm is gently lifted and as it breaks contact with the skin, the characteristic "crunching" sound is produced (Fig. 11). To create a more realistic effect, rhythmic light pressure and elevation must be employed to produce the typical three components similar to those produced by a pericardial friction rub. Rales can be simulated by lifting the chest piece very slowly to prolong releasing the skin-diaphragm contact.

Discussion

The quality of reproduction is surprisingly good especially if no electronic amplifiers are interspaced between the stethoscope and the observer's ears. The "phonocardiograms" accompanying the figures were

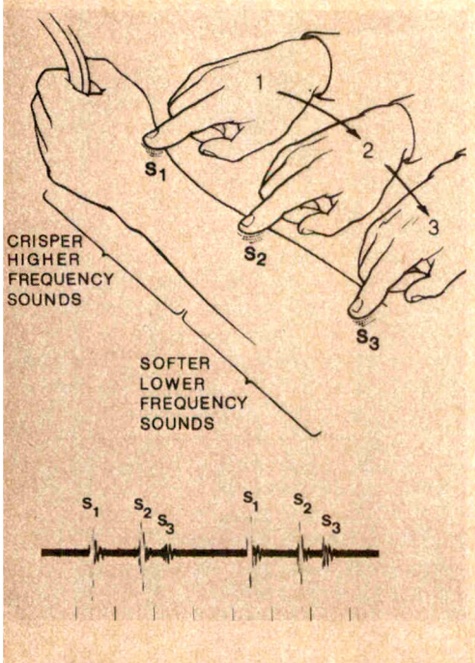


FIGURE 2 (left). Sequential tapping with the index finger produces the first (S_1) and second (S_2) heart sounds and a ventricular diastolic gallop (S_3). The intensity and quality of the sound produced depend upon the area tapped and the vigor of the tap.

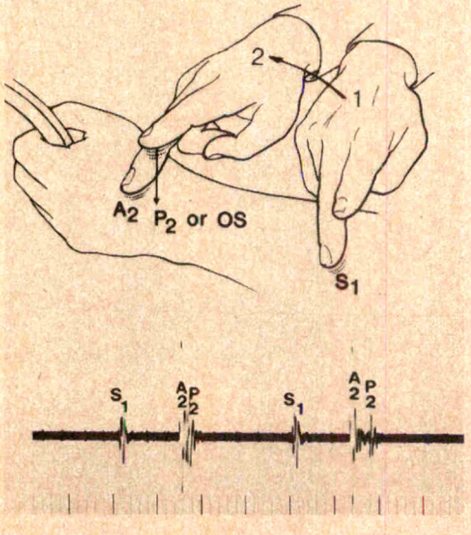


FIGURE 3 (right). Tapping first with the middle finger and then the middle finger and index finger in rapid succession produces the first heart sound and both the aortic (A_2) and pulmonary (P_2) components of the second heart sound or the aortic component and opening snap (OS), depending upon the interval. Respiratory variation of splitting of the second sound is easily produced by changing the interval between the middle and index finger taps.

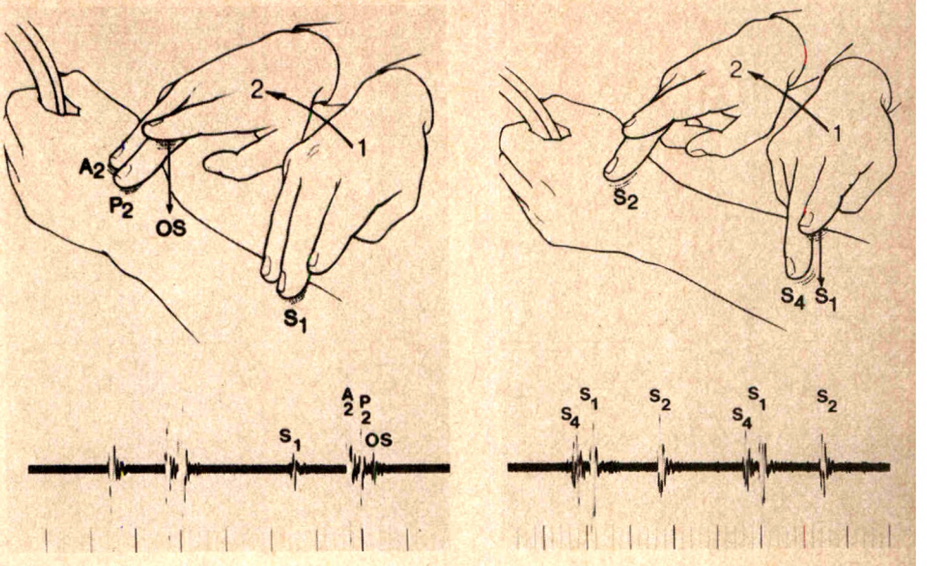


FIGURE 4 (left). The triple sound of the aortic valve closure (A_2), pulmonary valve closure (P_2) and mitral opening snap (OS) is produced by sequentially tapping with the ring, middle and index fingers.

FIGURE 5 (right). The rhythm of an atrial diastolic gallop (S_4) is produced by first tapping sequentially with the middle and index fingers over the upper forearm and then giving a single tap over the wrist.

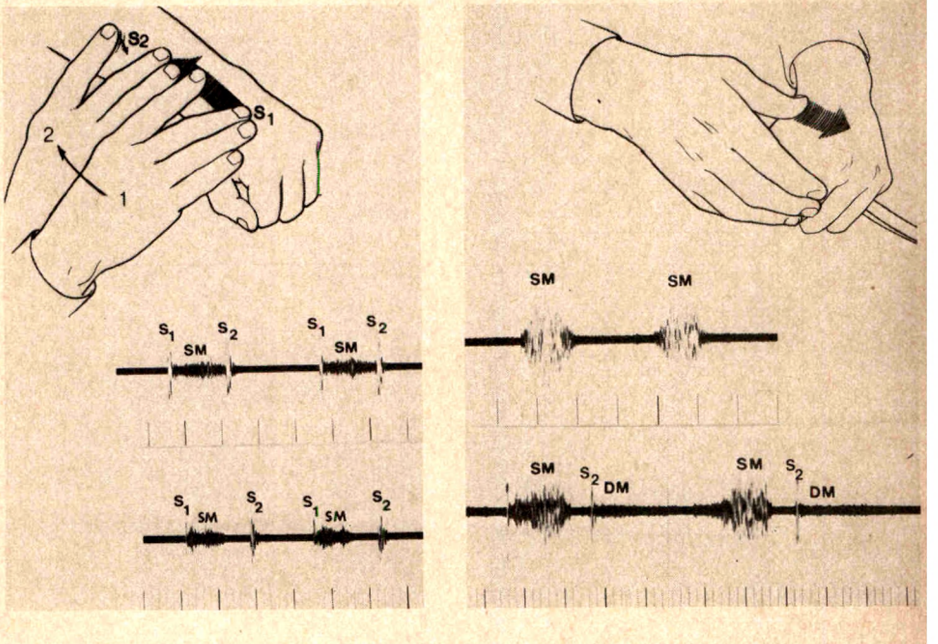


FIGURE 6 (left). A holosystolic murmur (SM) is created by softly dragging the middle and ring ringers across the back of the hand and wrist, terminating the motion by tapping the index finger (top "phonocardiogram"). A less than holosystolic murmur is created by performing the entire maneuver with just the index finger (bottom "phonocardiogram"). SM = systolic murmur.

FIGURE 7 (right). A harsh systolic murmur (SM) is produced by pushing the thumb across the back of the hand. A soft diastolic murmur (DM) is produced by softly dragging the thumb back to the original position. The change in direction of the thumb motion may, but does not invariably, produce a skin "pop" that simulates the second heart sound.

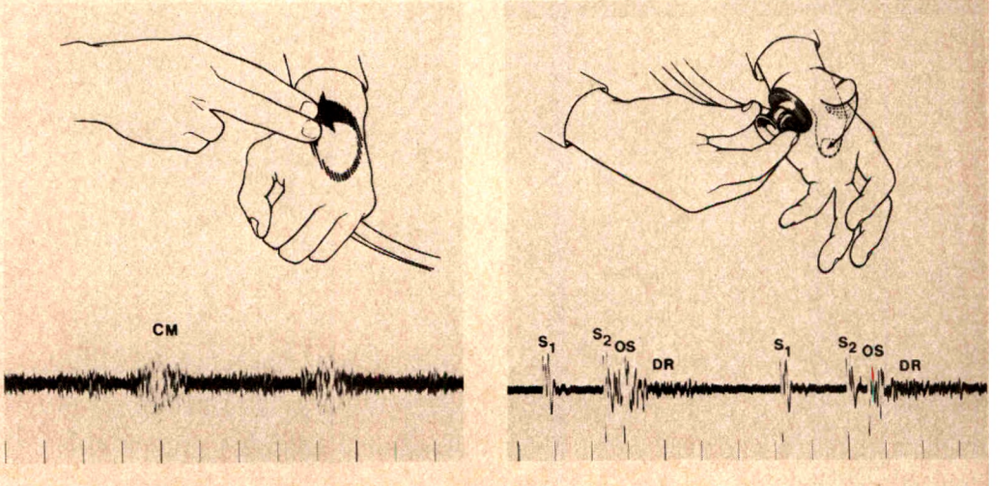
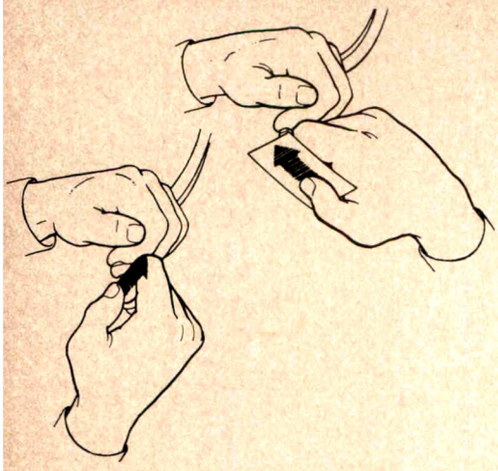


FIGURE 8 (left). A continuous murmur (CM) is produced by rubbing the hand in a circular fashion with light and firm pressure in alternating halves of the circle. The alternating pressure creates the crescendo and decrescendo portions of the murmur.

FIGURE 9 (right). The diastolic rumble (DR) of mitral stenosis is simulated by the muscle tremor produced by flexing the thumb. The addition of the first and second heart sounds and opening snap (OS) is as shown in Figure 3 and requires that the chest piece be rested upon a stable surface or held by an observer.



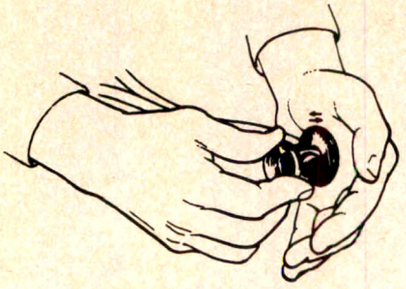


FIGURE 10 (left). A leathery pleural friction rub is produced by rubbing the thumb and index finger together. The sound is transferred to the hand holding the stethoscope by touching the hands together. Pinching the index card between the thumb and index finger while performing the maneuver will provide additional friction if necessary to produce the desired effect.

FIGURE 11 (right). The sound of mediastinal emphysema is produced by allowing the diaphragm to stick to the palm then rhythmically applying light pressure and elevation to break the diaphragm-skin contact.

recorded on a Cambridge physiologic recorder using the techniques described and differ little from those produced by actual heart sounds. The authenticity of the simulated sounds produced is probably related to the similarity between the tissue vibration and sound conduction in this technique and those encountered in the production of physiologic heart sounds. The amount of practice required to master the method varies. It may be necessary to experiment with the described techniques and to modify them while listening to the sounds produced before transferring the stethoscopic earpiece to the student. A stethoscope with multiple head sets provides the easiest means for the person producing the sounds to monitor his efforts.

In summary, the technique provides an inexpensive versatile, highly portable heart sound simulator readily available at any medical facility.

Acknowledgment

I thank Drs. Jack B. Taylor, William C. Roberts and W. Proctor Harvey for their encouragement during the development of this technique. I also thank Mrs. Trudy Nicholson for her skillful assistance in preparation of the illustrations.

Effects of Glucose-Insulin-Potassium on Myocardial Substrate Availability and Utilization in Stable Coronary Artery Disease

Studies on Myocardial Carbohydrate, Lipid and Oxygen Arterial-Coronary Sinus Differences in Patients with Coronary Artery Disease

ALFRED W. STANLEY, Jr., MD, FACC
ROGER E. MORASKI, MD
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Birmingham, Alabama

To assess the metabolic effects of myocardial substrate alteration in patients with coronary artery disease, glucose-insulin-potassium solution was administered intravenously for 30 minutes to 14 men with stable angiographically documented coronary artery disease. The glucose-insulin-potassium solution (300 g of glucose, 50 units of regular insulin and 80 mEq of potassium chloride per liter of water) was infused at a constant rate in each patient, but individual infusion rates ranged from 0.013 to 0.032 ml/kg per min (4 to 10 mg glucose/kg per min) in the 14 patients. Simultaneous arterial and coronary sinus samples were obtained at 15 minute intervals during a stable 30 minute control period and again at 15 minute intervals during the infusion; samples were assayed for glucose, lactate, free fatty acid and oxygen content.

In all 14 patients, during the glucose-insulin-potassium infusion, arterial glucose and lactate increased and arterial free fatty acid levels fell; the magnitude of the changes in arterial lactate and free fatty acids was related to the rate of infusion. Arterial-coronary sinus differences ($A\text{-}C_s$) for glucose, lactate and free fatty acid levels correlated with the arterial concentrations of these substrates ($r = 0.66$, 0.87 and 0.79, respectively). Regression analyses demonstrated myocardial thresholds for the uptake of these substrates as follows: glucose 79 mg/100 ml; lactate 300 μmole/liter; and free fatty acids 100 to 200 μEq/liter. Finally and most importantly, the reduction in $A\text{-}C_s$ oxygen values after glucose-insulin-potassium infusion correlated with the reduction in $A\text{-}C_s$ free fatty acid levels ($r = 0.64$, $P < 0.0001$). This observation suggests that, in patients with coronary artery disease, glucose-insulin-potassium infusion may significantly diminish myocardial oxygen requirements by reduction of myocardial free fatty acid utilization and simultaneous enhancement of myocardial carbohydrate utilization.

Myocardial substrate availability may be an important determinant of myocardial oxygen demand in patients with coronary artery disease. Infusion of glucose-insulin-potassium solution has the potential to alter myocardial substrate availability, thus improving the balance between myocardial oxygen demand and supply.

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The myocardium has the potential to utilize a variety of metabolic fuels as its energy substrate—glucose, pyruvate, lactate, free fatty acids, ketones and amino acids; however, it has been repeatedly shown that in the fasting state the primary myocardial metabolic energy substrate consists of free fatty acids and that free fatty acid oxidation accounts for approximately 60 percent of myocardial oxygen

needs.[1] Recent studies suggest that free fatty acids may not be the optimal substrate for the hypoxic myocardium. It has been shown in animal models that increased levels of free fatty acids can increase myocardial oxygen utilization by 10 to 25 percent[2–6] and inhibit glucose utilization.[7,8] Furthermore, Kurien and Oliver[9] have proposed that free fatty acids may exert toxic arrhythmogenic effects on the hypoxic myocardium.

Glucose, on the other hand, would appear to be a more beneficial substrate in the setting of myocardial hypoxia. Evans et al.[10] demonstrated that the hypoxic heart utilizes greater quantities of glucose than the well oxygenated heart. Morgan et al.[11,12] and Post et al.[13] showed that glucose uptake by the heart is not maximal at normal blood levels and can be accelerated by both insulin and hypoxia. Along with these studies documenting an increase in glucose uptake during hypoxia, additional animal investigations indicated that glucose-enriched solutions could improve myocardial electrical[14,15] and mechanical[15,16] performance, maintain cellular ultrastructure,[15] promote myocardial recoverability,[15–17] preserve intracellular adenosine triphosphate (ATP) concentrations,[17] reduce myocardial creatinine phosphokinase depletion[18] and retard mitochondrial injury during hypoxia.[18,19] Maroko et al.[20] have reported that infusion of glucose-insulin-potassium could preserve myocardium after experimental myocardial infarction.

Glucose-insulin-potassium infusions in the clinical setting of acute myocardial infarction have been shown to dramatically reduce serum free fatty acid levels,[21,22] but there have been no detailed studies of the interrelation of myocardial carbohydrate and free fatty acid metabolism in patients with documented coronary artery disease given infusions of glucose-insulin-potassium solution. Accordingly, this investigation was undertaken to measure the effect of glucose-insulin-potassium infusion on myocardial arterial-coronary sinus ($A\text{-}C_s$) differences of glucose, lactate, free fatty acids and oxygen in patients with stable coronary artery disease.

Methods

Patient Population and Catheterization Procedure

Fourteen men aged 37 to 65 years were admitted for evaluation of coronary artery disease. None of the patients had clinical diabetes mellitus, as assessed by a 3 hour glucose tolerance test; all medications were discontinued on admission. The catheterization procedure and metabolic protocol were described to each patient, and informed consent was obtained. No patient was permitted caloric intake or premedication during the 12 hours preceding catheterization. Each patient was subsequently found by coronary angiography to have significant coronary artery disease, defined as one or more stenoses of greater than 50 percent in a major coronary artery.

After local anesthesia with 1 percent lidocaine, a small Teflon® catheter was introduced percutaneously into the left brachial artery and positioned in the left subclavian artery. The left brachial vein was isolated, and a catheter was advanced into the coronary sinus under fluoroscopic guidance. The catheter tip was positioned more than 1 cm beyond the estimated location of the ostium of the coronary sinus after documentation of catheter placement by oximetry and fluoroscopy. Patency of the catheter was maintained by continuous infusion of isotonic saline solution. The right brachial vein was then cannulated for the infusion of the glucose-insulin-potassium solution. During the control period, isotonic saline solution was used to maintain patency of this catheter; no patient received heparin during the study. Heart rate and intraarterial pressure were monitored during the 30 minute control and infusion periods.

Glucose-Insulin-Potassium Administration and Sample Collections

After the catheters were positioned in the brachial artery and in the coronary sinus, the metabolic protocol was initiated. The protocol consisted of a 30 minute control period and 30 minutes of infusion of glucose-insulin-potassium solution. During the control period, isotonic saline solution was used to maintain the catheters patent, and the arterial and coronary sinus catheters were flushed at 5 minute intervals throughout the 60 minute study. Simultaneous arterial and coronary sinus samples were drawn at 15 and 30 minutes during the control period and similarly at 15 and 30 minutes during the period of glucose-insulin-potassium infusion. The first 5 ml of each sample was discarded, and 20 ml of blood was then withdrawn for determination of glucose, lactate and free fatty acid levels. An additional 10 ml for oxygen content was subsequently collected, which resulted in a total of 70 ml for each interval of sampling or 35 ml from the arterial and coronary sinus catheters, respectively.

After collection of the second sample at 30 minutes of the control period, 10 g of glucose and 5 units of regular insulin were injected into the right brachial vein. This injection was followed immediately by continuous infusion of glucose-insulin-potassium (300 g of glucose, 50 units of regular insulin and 80 mEq of potassium chloride per liter of water). The pH of the solution was 4.5, and the osmolality was 1,827 milliosmoles. Each of the 14 patients received this concentration of glucose-insulin-potassium at a constant rate throughout the 30 minute infusion period. However, the rate of infusion ranged from 0.013 to 0.032 ml/kg per min (or 4 to 10 mg glucose/kg per min) in individual patients. Six patients received the solution at a rate of 0.013 to 0.020 ml/kg/min (4 to 6 mg glucose/kg per min), and eight patients at a rate of 0.020 to 0.032 ml/kg per min (7 to 10 mg glucose/kg per min). Fifteen minutes after the start of glucose-insulin-potassium infusion, simultaneous arterial and coronary sinus samples were drawn; similar samples were also drawn at 30 minutes. The amount of blood removed during the metabolic period was similar to the amount of isotonic saline solution infused. After the final blood samples were collected, the metabolic study was terminated, and the patients underwent right and left heart catheterization with coronary arteriography and left ventriculography.

Assay Methods

Lactate: 6.5 ml of 6 percent perchloric acid was added to 2 ml of blood immediately upon withdrawal from the patient. The tubes were weighed before and after addition of the blood to determine the exact amount added. Tubes

were then centrifuged at 6,000 × *g* for 30 minutes to remove the precipitated protein. The perchloric acid extract was titrated to pH 4.5 with 1 molar potassium hydroxide at 0°C with agitation. Thirty minutes later, precipitated potassium perchlorate was removed from the mixture by centrifugation at 6,000 × *g* for 15 minutes. The supernatant was then assayed for lactate spectrophotometrically by standard enzymatic methods.[23]

Glucose and free fatty acids: Blood was collected in chilled tubes containing sodium ethylenediaminetetraacetic acid (EDTA) to prevent clotting. The tubes were centrifuged at 600 × *g* for 30 minutes and the plasma was assayed for glucose according to the glucose oxidase and ferrocyanide method of Hall and Tucker.[24] Free fatty acid levels were determined by modification of the Dole procedure.[25] Appropriate standards were run with each assay. Coefficients of variance for this laboratory are 3 percent for lactate, 1 percent for glucose and 5 percent for free fatty acids.

Oxygen content: Samples were collected in plastic syringes containing 0.5 ml of heparin (10,000 units/ml) and were immediately placed in ice. Oxygen content was determined by the Van Slyke manometric technique.

Data Analysis and Statistical Methods

The 15 and 30 minute arterial and coronary sinus blood samples for glucose, lactate, free fatty acids and oxygen during the control period were averaged to yield a single control value for each substance. The coronary sinus measurement of each substance was subtracted from the arterial value to give the myocardial arterial-coronary sinus (A-C_s) difference. The arterial values for glucose, lactate and free fatty acids were compared with the respective myocardial A-C_s differences of each substance for both the control and glucose-insulin-potassium infusion periods. The paired *t* test was used to test the significance of the difference between samples obtained during the control and infusion periods. Standard least square techniques were used to obtain the correlations and regression lines for the lactate and free fatty acid measurements. A nonlinear least square analysis was found empirically to describe the relation between arterial glucose and A-C_s glucose better than the linear relation between the untransformed variables.[26]

TABLE I

Serum Osmolality

Case no.	Infusion Rate (mg glucose/ kg per min)	Control* (milliosmoles)	GIK† (milliosmoles)
1	6.0	282	284
2	7.8	286	283
3	9.4	286	286

* The control sample was an arterial sample drawn at 15 minutes during the 30 minute control period.

† The second sample was drawn 15 minutes after the start of the glucose-insulin-potassium infusion.

Results

Circulatory dynamics and serum osmolality All patients remained comfortable during the control and infusion periods without apparent apprehension or chest pain. Heart rate and arterial pressure remained stable throughout the study.

The elevation in blood glucose levels with the glucose-insulin-potassium solution is not enough to increase significantly serum osmolality on a theoretical basis, and measurements of serum osmolality in three patients did not change significantly (Table I).

Arterial glucose concentration and myocardial glucose A-C_s difference: Infusion of glucose-insulin-potassium solution increased arterial concentrations at 15 and 30 minutes in 13 of the 14 patients (Fig. 1). In six patients (Group I) the solution was infused at a low rate (4 to 6 mg glucose/kg per min). In eight patients (Group II) the infusion rate was high (7 to 10 mg glucose/kg per min). The mean arterial concentration of glucose was higher at 15 minutes than at 30 minutes in both groups. As arterial glucose concentration increased, myocardial glucose arterial coronary sinus (A-C_s) difference increased (Fig. 1) and the relation between these measurements appeared to obey first order kinetic laws (Fig. 2). The mean myocardial glucose A-C_s difference was simila

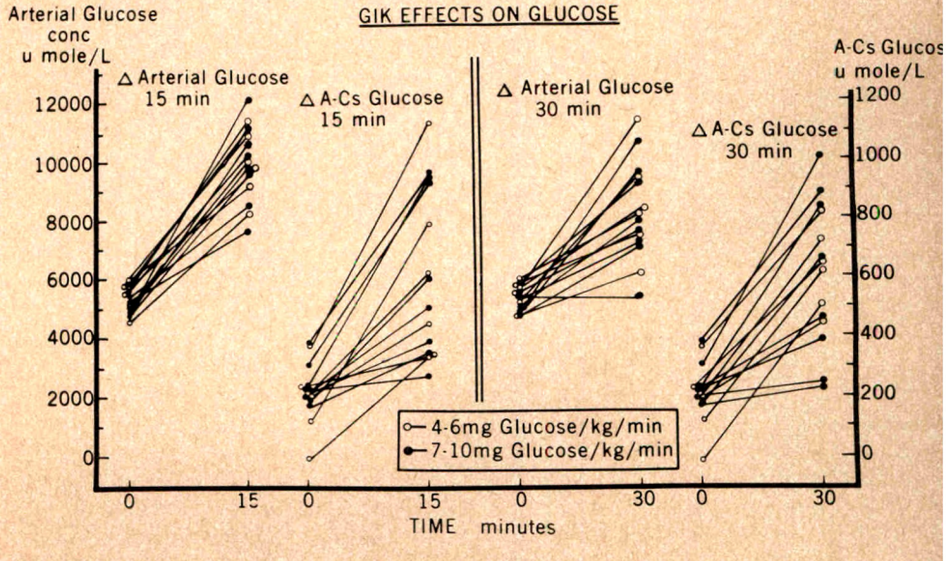

FIGURE 1. Simultaneous alterations in arterial concentration and myocardial arterial-coronary sinus (A-C_s) difference for glucose after 15 **(left)** and 30 **(right)** minutes of infusion of glucose-insulin-potassium (GIK). The **open circles** indicate patients in Group I (low rate of infusion) and the **closed circles** those in Group II (high rate of infusion).

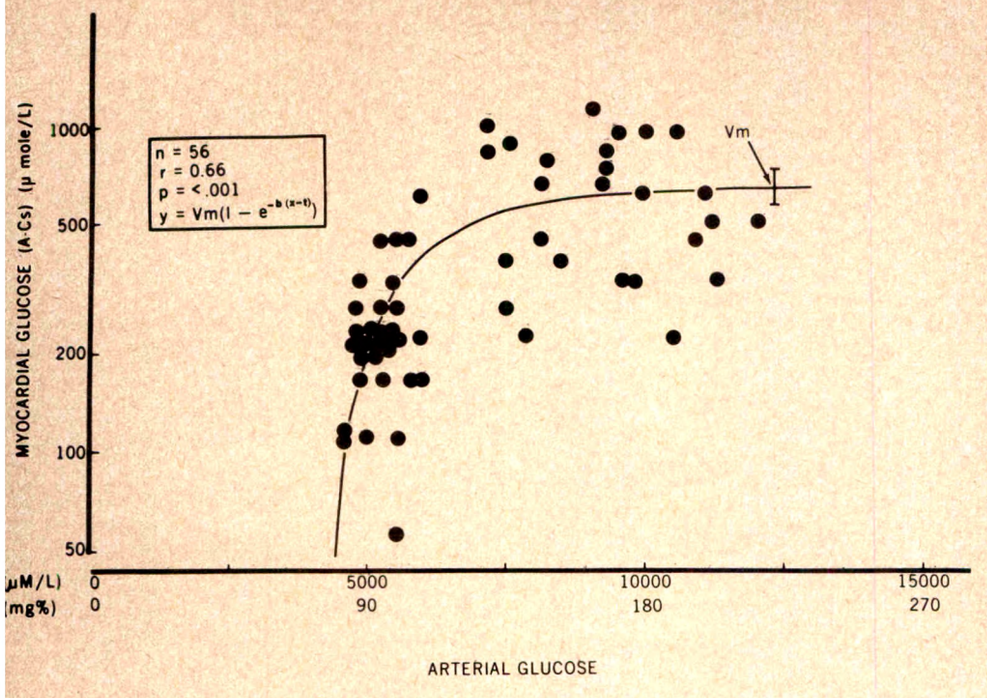

FIGURE 2. Relation between arterial glucose concentration and myocardial A-C_s difference for glucose during control and glucose-insulin-potassium infusion periods. Because the general exponential relation shown described the observed data better than a simple linear fit (r = 0.66 versus r = 0.56), a semi-log plot is depicted to better demonstrate the apparent exponential relation between the two variables. The arterial glucose "threshold" (t) for myocardial glucose uptake, determined by the intercept of the above plot with the abscissa, is 4,400 μmoles/liter or 79 mg/100 ml glucose. The K_m, or arterial glucose concentration associated with 1/2 V_m is 5500 μmole/liter or 99 mg/100 ml glucose, where V_m is the maximal A-C_s glucose value. The constant b describes the curve shape. n = number of patients; p = probability; r = correlation coefficient.

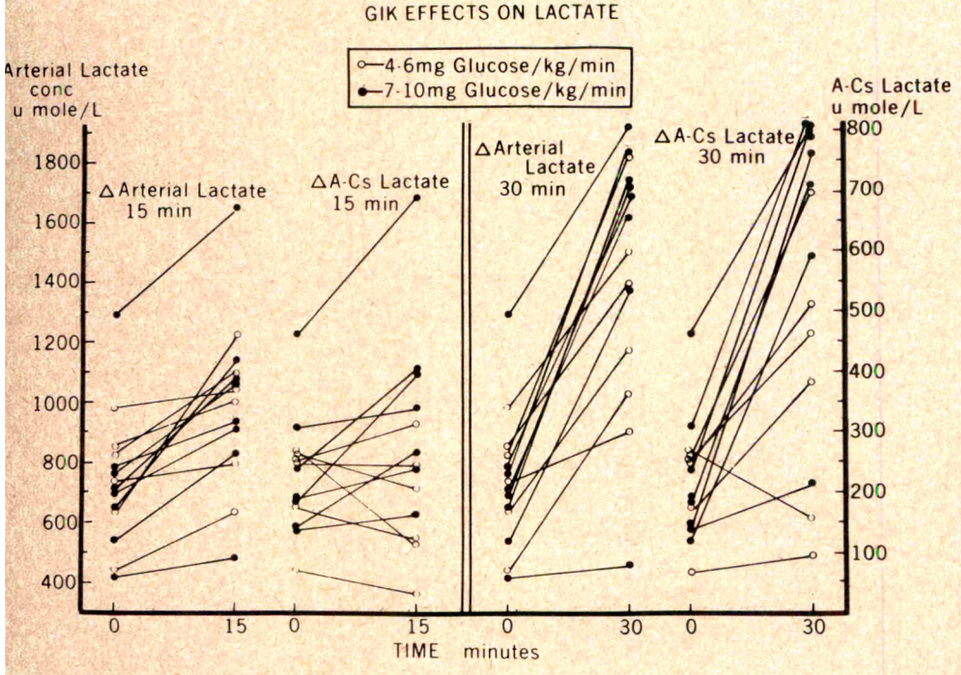

FIGURE 3. Simultaneous changes in arterial lactate concentration and myocardial A-C_s difference for lactate after 15 and 30 minutes of glucose-insulin-potassium (GIK) infusion. The **open** and **closed circles** represent, respectively, groups with a low and high infusion rate.

at 15 and 30 minutes in both groups of patients. Although the infusion rate and the amount of glucose delivered was lower in Group I than in Group II, the ratio of glucose to insulin and potassium remained the same in both groups. Alterations in myocardial glucose A-C_s difference were not related to alterations in myocardial oxygen extraction (r = 0.192).

Arterial lactate concentration and myocardial lactate A-C_s difference: Arterial lactate concentration was increased in all patients after infusion of glucose-insulin-potassium (Fig. 3), and was a function of both rate and duration of infusion. The high infusion rates (7 to 10 mg glucose/kg per min) produced a greater elevation in arterial lactate concentration at both 15 and 30 minutes than did the low infusion rates (4 to 6 mg glucose/kg per min). The mean arterial lactate increase in eight patients receiving the solution at high infusion rates was 41 percent at 15 minutes (P <0.01) and 113 percent at 30 minutes (P <0.01). In the six patients receiving the solution at low rates of infusion there was a mean increase in arterial lactate of 30 percent at 15 minutes

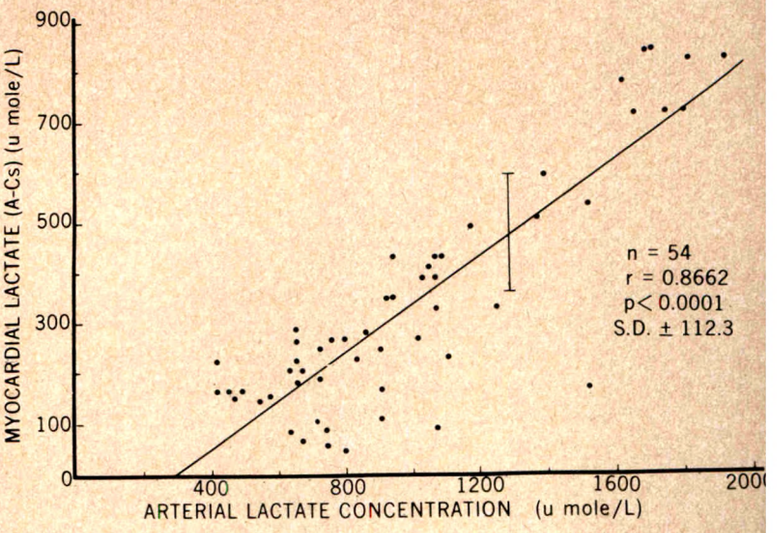

FIGURE 4. Relation between arterial lactate concentration and myocardial lactate A-C_s difference during the control and glucose-insulin-potassium infusion periods. S.D. = standard deviation.

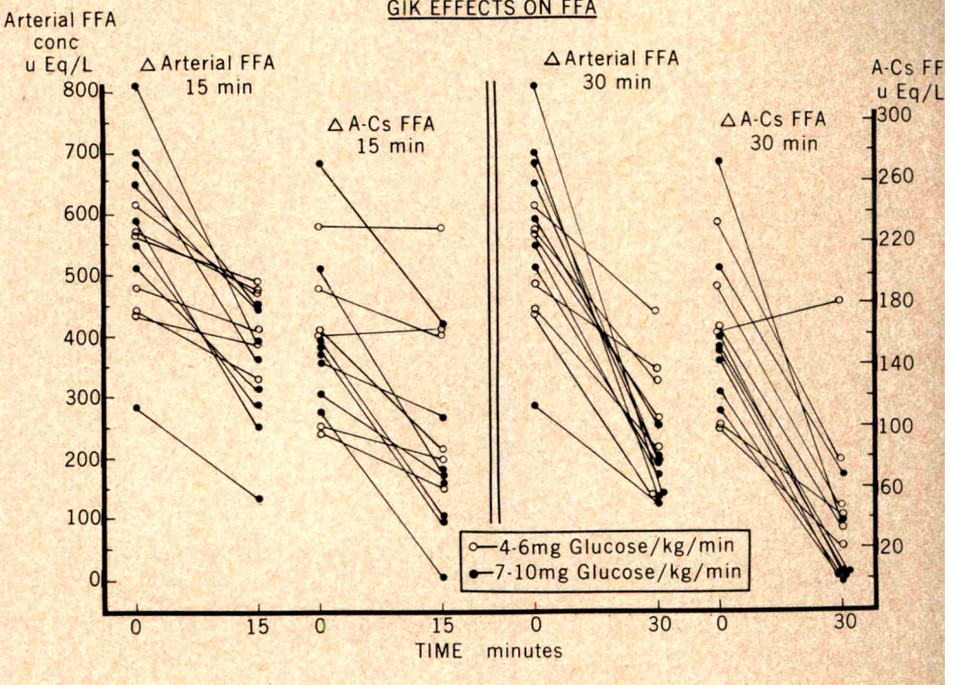

FIGURE 5. Simultaneous changes in arterial free fatty acid (FFA) concentration and myocardial free fatty acid A-C_s difference after 15 and 30 minutes of glucose-insulin-potassium infusion. The **open** and **closed circles** represent, respectively, the groups with a low and high rate of infusion.

(P <0.05) and 80 percent at 30 minutes (P <0.01). All patients at rest demonstrated higher arterial lactate concentrations than coronary sinus concentration in samples obtained at both 15 and 30 minutes during the control period. In patients receiving glucose-insulin-potassium solution at the low infusion rate (Group I) there was a mean 28 percent reduction in lactate A-C_s difference at 15 minutes and a 79 percent increase in lactate A-C_s difference at 30 minutes, but neither of these measurements was significantly different from control values. In patients receiving the solution at the high infusion rate (Group II), the mean lactate A-C_s difference increased 60 percent at 15 minutes (P <0.05) and 200 percent at 30 minutes (P <0.01).

Myocardial lactate A-C_s difference was linearly related to arterial lactate concentration (r = 0.84) (Fig. 4). Mean lactate A-C_s difference in the two groups differed at both 15 minutes (P <0.05) and 30 minutes (P <0.05) but there was no correlation between myocardial lactate A-C_s difference and myocardial oxygen extraction (r = 0.452).

Arterial free fatty acid concentration and myocardial free fatty acid A-C_s difference. Infusion of glucose-insulin-potassium consistently suppressed arterial free fatty acid concentration (Fig. 5) and the extent of suppression was influenced by the rate and duration of infusion. Infusion at the high rate (7 to 10 mg glucose/kg per min) reduced arterial free fatty acid concentration more at 15 and 30 minutes than did the lower infusion rate of 4 to 6 mg glucose/kg per min. Both infusion rates depressed fr

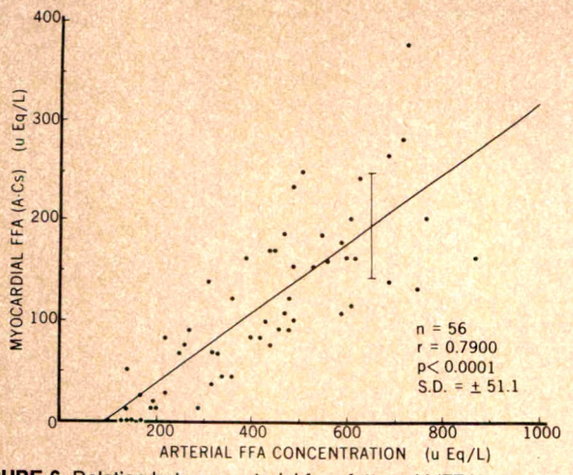

FIGURE 6. Relation between arterial free fatty acid (FFA) concentration and myocardial free fatty acid A-C_s difference during the control and glucose-insulin-potassium infusion periods. Arterial free fatty acid concentrations between 100 and 200 μEq/liter were associated with myocardial A-C_s differences approaching zero.

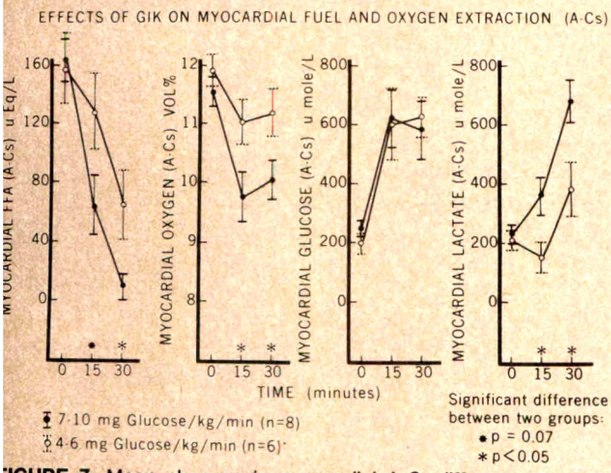

FIGURE 7. Mean changes in myocardial A-C_s difference after 15 and 30 minutes of glucose-insulin-potassium infusion. The alterations in lactate, free fatty acid and oxygen A-C_s differences were dependent on the duration and rate of infusion of glucose-insulin-potassium solution per unit of time. Myocardial glucose A-C_s differences appeared independent of both duration of infusion and the amount of glucose-insulin-potassium infused.

atty acid levels as a function of the duration of infusion, but the high infusion rate reduced the fatty cids more rapidly and to a greater extent than the ow infusion rate. The low infusion rate suppressed ree fatty acids 18 percent at 15 minutes (P <0.01) nd 45 percent at 30 minutes (P <0.01), and at high nfusion rates arterial free fatty acids were sup-ressed 45 percent at 15 minutes (P <0.01) and 71 ercent at 30 minutes (P <0.01) (Fig. 5).

The myocardial free fatty acid A-C_s difference was function of arterial free fatty acid concentration. he correlation coefficient is good (r = 0.79), and igure 6 demonstrates a linear relation between these wo measurements. All six patients in Group I (low nfusion rate) continued to demonstrate a persistent nyocardial A-C_s difference in free fatty acid levels after 30 minutes of glucose-insulin-potassium infusion, but the myocardial free fatty acid A-C_s difference was reduced to zero in three and near zero in four of eight patients in Group II (high infusion rate). The mean reduction in A-C_s free fatty acid was 94 percent in Group II as opposed to 57 percent in Group I (both P <0.01). The two groups were statistically separated (P <0.01) after 30 minutes of infusion (Fig. 7).

Myocardial A-C_s free fatty acid difference approached zero at arterial free fatty acid concentrations of 100 to 200 μEq/liter, thus, defining the threshold for myocardial free fatty acid uptake in fasting patients with stable coronary artery disease.

Myocardial A-C_s oxygen difference: Infusion of glucose-insulin-potassium reduced myocardial oxygen A-C_s difference in all 14 patients. This reduced oxygen arteriovenous difference was slightly greater at 15 minutes than at 30 minutes in both Group I and Group II (Fig. 7). This may be related to the initial bolus dose of glucose and insulin administered to all patients. In the six patients in Group I (low infusion rate) mean oxygen A-C_s difference was reduced from control levels by 7.6 percent at 15 minutes (P <0.05) and 6 percent at 30 minutes (P <0.05). In the eight patients in Group II mean myocardial oxygen A-C_s difference was reduced by 15.8 percent at 15 minutes (P <0.01) and 13.1 percent at 30 minutes (P <0.01). The two groups were statistically separated at 15 (P <0.05) and 30 minutes (P <0.05) (Fig. 7).

A significant relation was established between reduced myocardial free fatty acid A-C_s difference and reduced myocardial oxygen A-C_s difference (r = 0.64) (Fig. 8).

Discussion

This study of the effects of infusion of glucose-insulin-potassium solution on myocardial substrates in patients with stable coronary artery disease has yielded some important findings relative to myocardial glucose kinetics, lactate and free fatty acid metabolism, and oxygen uptake.

Myocardial glucose kinetics: Arterial glucose concentrations increased, and myocardial arterial-coronary sinus (A-C_s) differences widened with the glucose-insulin-potassium infusion. However, as predicted from the work of Morgan and Post et al.[11–13] on glucose transport kinetics, these variables revealed a curvilinear relation as shown in Figure 2. In the isolated perfused heart, glucose transport is the rate-limiting step in glucose utilization; elevated blood sugar levels facilitate myocardial glucose utilization because glucose transport is not maximal at normal blood glucose levels.[11–13] Insulin increases the glucose utilization by alterations in membrane kinetics so that glucose transport is accelerated at normal blood sugar levels.

The present observations in patients with stable coronary artery disease indicate that the myocardial glucose A-C_s differences were independent of the rate and duration of glucose-insulin-potassium infusion.

The k_m of glucose transport (arterial glucose concentration associated with half the maximal glucose A-C_s difference) plotted from Figure 2 is 5.5 millimolar (plasma glucose of 99 mg/100 ml); this value agrees with the value obtained in animal models.[11–13] Assuming 1 ml/min per g of myocardium for coronary blood flow, the maximal velocity for glucose transport calculated from the data in Figure 2 is 7 mg/g of heart muscle per hour. The threshold for glucose uptake is 4.4 millimolar (79 mg/100 ml). These data suggest that modest changes in the arterial glucose level alter greatly the uptake of glucose by the heart.

Myocardial lactate metabolism: Arterial lactate concentrations increased during the infusion of the glucose-insulin-potassium solution. Kreisberg[27] has shown that glucose accounts for 50 to 70 percent of lactate production in man with the major production sites being skeletal muscle and erythrocytes. Lactate increases whenever the rate of glycolysis exceeds the rate of oxidation.[28] Although lactate production is known to develop during periods of hypoxia and as various cellular oxidation reduction systems shift toward a more reduced state,[29–32] increased pyruvate production can produce changes in lactate production unassociated with hypoxia.[33] Arterial lactate concentration was greater in Group II (high infusion rate) than in Group I. Arterial lactate concentrations changed with time and were greater at 30 minutes than at 15 minutes in both groups. All subjects had higher values for lactate in arterial than in coronary sinus samples, but none experienced chest pain during the control period. Patients continued to extract lactate in increasing amounts after 30 minutes of infusion.

Myocardial lactate A-C_s differences were linearly related to arterial lactate concentrations, as previously reported in dogs.[29] The regression equation relating arterial lactate concentration to myocardial lactate A-C_s difference suggests a resting threshold for lactate uptake corresponding to arterial lactate levels of 300 μmole/liter.

Myocardial free fatty acid metabolism: The observed reduction in arterial free fatty acid concentrations is considered a reflection of the glucose-insulin-potassium infusion-induced stimulation of free fatty acid uptake and esterification. This process occurs primarily in adipose tissue by the provision of activated glycerol.[34–37] Reduction in free fatty acid levels occur when glyceride synthesis is relatively greater than lipolysis. Glucose and insulin have been demonstrated to inhibit net fatty acid release from adipose tissue in fasted animals.[38] Bailey et al.[36] and Raben and Hollenberg[39] obtained evidence that glucose reduces free fatty acid levels by favoring triglyceride synthesis and not by the inhibition of lipase action.

In this study, with the inhibition of free fatty acid production, arterial concentrations rapidly declined, consistent with estimated turnover rates for plasma free fatty acids.[40,41] As arterial free fatty acids decreased in these subjects, the myocardial A-C_s free fatty acid differences were reduced in a linear manner (Fig. 6). The linear relation between arterial fre
fatty acids and myocardial A-C_s free fatty acid differ
ences was similar to earlier findings in experimenta
animals and in normal resting man.[42–46] After 3
minutes of glucose-insulin-potassium infusion, th
A-C_s free fatty acid difference was reduced to zero i
three and near zero in four of the eight patients i
Group II (high infusion rate). The X intercept of th
regression line suggests a threshold for myocardi
free fatty acid extraction in patients with coronar
artery disease at arterial free fatty acid concentratio
of 100 to 200 μEq/liter. Carlsten et al.[47] have demor
strated a myocardial free fatty acid threshold of 35
μEq/liter in healthy human subjects, and observa
tions from animal experiments[42,43] have suggested
free fatty acid threshold of 100 μEq/liter. Howeve
even at the point where there is no measurable A-(
free fatty acid difference, there may still be some u
take of free fatty acids, which is balanced by fr
fatty acid release by the heart.[44]

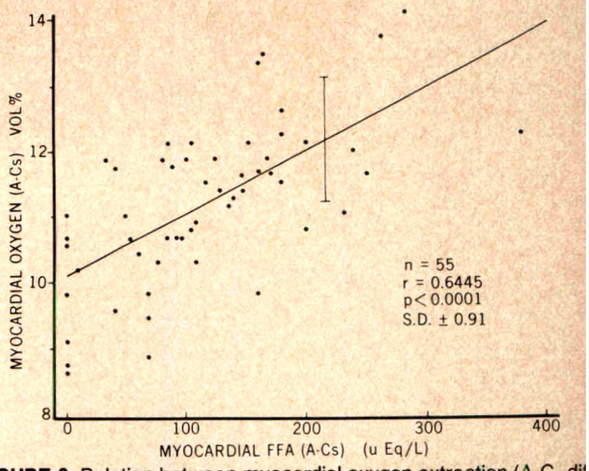

FIGURE 8. Relation between myocardial oxygen extraction (A-C_s dif
ference) and myocardial free fatty acid (FFA) A-C_s difference durin
the control and glucose-insulin-potassium infusion periods.

**Myocardial oxygen uptake after infusion o
glucose-insulin-potassium:** A decrease in myoca
dial A-C_s oxygen difference occurred during the gl
cose-insulin-potassium infusion period. This redu
tion in myocardial A-C_s oxygen difference occurre
in all 14 patients but was more pronounced in Grou
II (high infusion rate) than in Group I (Fig. 7). A si
nificant correlation between increasing myocardi
free fatty acid utilization and enhanced myocardi
oxygen consumption has previously been demo
strated in studies in which arterial free fatty ac
concentrations were elevated experimentally.[2–6] El
vated free fatty acid levels can increase the myoca
dial oxygen utilization by 10 to 26 percent.[2–6]

The increased oxygen consumption produced b
elevated levels of arterial free fatty acids may occ
by several mechanisms. Free fatty acids may increa
oxygen utilization by uncoupling oxidative phosph
rylation or by inhibition of glycolysis so that aden
sine triphosphate (ATP) generation by substra
level phosphorylation would not be available.[48–50] F

comparison with carbohydrate oxidation, free fatty acid oxidation theoretically produces slightly less ATP per mole of oxygen consumed. Furthermore, in states of free fatty acid excess, additional ATP is utilized for the esterification of free fatty acids.[51] In the isolated perfused liver, Williamson et al.[51] observed that the esterification of free fatty acids and the decreased efficiency of beta oxidation could account for the increase in oxygen uptake by the liver when it was perfused with free fatty acids. If esterification is decreased as free fatty acid uptake diminished, ATP requirements could be reduced with subsequent reductions in oxygen utilization.

Clinical Implications

The present study in which a glucose-insulin-potassium solution was infused in patients with stable coronary artery disease has yielded several observations that may be of potential benefit to patients with the unstable manifestations of coronary artery disease. As previously mentioned, recent data suggest that free fatty acids may be an unfavorable substrate for hypoxic myocardium; our data show that dramatic reduction of arterial free fatty acids can be achieved with infusion of glucose-insulin-potassium in patients with stable coronary artery disease. Furthermore, when arterial free fatty acid levels are reduced to 200 μEq/liter or less—the myocardial "threshold" for free fatty acids—the A-C_s free fatty acid difference approaches zero. Minimal infusion rates of glucose-insulin-potassium (300 g of glucose, 50 units of regular insulin, 80 mEq of potassium chloride per liter of water) that reduced the A-C_s free fatty acid difference to zero were rates of 0.025 ml/kg per min (1.5 ml/kg per hr or 8 mg of glucose/kg per min).

The data further demonstrate that the A-C_s free fatty acid reduction is accompanied by increased A-C_s carbohydrate (glucose and lactate levels). This shift in myocardial substrate uptake from free fatty acid to carbohydrate is accompanied by a significant fall in A-C_s oxygen. That the reduction in A-C_s oxygen reflects a fall in myocardial oxygen consumption cannot be ascertained with certainty from the available data since coronary blood flow was not measured. There is, however, no reason to suspect that coronary flow was altered during the study, since all patients remained in a stable state throughout the procedure without appreciable changes in heart rate or intraarterial pressure. Furthermore, a recent study in dogs report that infusion of glucose-insulin-potassium decreased myocardial oxygen consumption without altering myocardial blood flow.[52] Thus it is reasonable to postulate that, in the present study, myocardial blood flow was constant, and the observed reduction in A-C_s oxygen is indicative of a decrease in myocardial oxygen consumption.

The potential of glucose-insulin-potassium infusion to reduce myocardial oxygen uptake while decreasing free fatty acid utilization and increasing glucose availability suggests that myocardial substrate availability and utilization may be a major clinically unappreciated determinant of myocardial oxygen consumption. However, it can be argued that infusion of glucose-insulin-potassium might reduce myocardial oxygen consumption by depression of myocardial contractility, a known major determinant of myocardial oxygen consumption.[53] Such an argument seems unreasonable in view of reported studies showing a beneficial effect of glucose-insulin solutions on myocardial performance, both in the experimental animal preparation[54,55] and, more recently, in patients after an acute myocardial infarction.[56]

Metabolic interventions such as infusion of glucose-insulin-potassium that alter myocardial substrate availability and metabolism require further exploration in patients with unstable manifestations of coronary artery disease.

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Metabolism of Free Fatty Acids, Glucose and Catecholamines in Acute Myocardial Infarction

Relation to Myocardial Ischemia and Infarct Size

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The myocardial metabolism of free fatty acids, glucose and catecholamines is reviewed in relation to current trends in the therapy of experimental myocardial infarction. Major modifications in the metabolism of free fatty acids, glucose and catecholamines have already been found after acute myocardial infarction in man, and animal experimental data suggest that such metabolic changes might play a role in the modification of infarct size and sometimes in the development of arrhythmias. However, animal experiments often represent extreme situations and the therapeutic use in man of agents to modify the metabolism of free fatty acids, glucose or catecholamines after myocardial infarction needs intensive investigation before general application. The sum total of the evidence from animal experiments suggests that increased circulating concentrations of free fatty acids and catecholamines, if sufficiently high, may be harmful rather than helpful to the outcome of acute myocardial infarction, and that increased provision of glucose (as glucose, insulin and potassium) may be beneficial. Reservations to these conclusions are that the concentrations used appear to be important factors in catecholamine and free fatty acid effects, and that the mechanism of action of glucose-insulin-potassium is more complex than originally thought.

Among the major metabolic changes described in patients with acute myocardial infarction are increased circulating blood free fatty acid concentrations,[1] glucose intolerance[2] and increased secretion of catecholamines.[3] It has been thought that each of these metabolic abnormalities might adversely influence the outcome of acute myocardial infarction, either by provoking arrhythmias or by adversely affecting the survival of ischemic tissue.[4,5] The purpose of this review is to evaluate the evidence for the participation of such metabolic factors in influencing the outcome of the infarction process and the development of arrhythmias.

I. Free Fatty Acids (FFA)

FFA Metabolism in Patients with Acute Myocardial Infarction

Free fatty acid concentrations in blood may be much increased in patients with acute myocardial infarction and are generally higher in patients who are more seriously ill.[1,6,7] An important cause of the increased blood levels is thought to be increased catecholamine activity (see later), which liberates free fatty acids from adipose tissue.[8] Starvation may be another factor because patients in acute pain generally do not eat much, and glucose given intravenously[5,6] lowers the elevated circulating free fatty acid levels. In four studies[1,6,9,10] patients with the highest circulating concentrations were more likely to have serious arrhythmias or other complications, but five other studies[11–15]

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failed to find this association. Furthermore, injections of heparin, which are known to increase blood levels of free fatty acids, do not appear to increase arrhythmias in patients with acute myocardial infarction.[6,13,16]

Thus, at present opinions differ as to whether the increased free fatty acid concentration found in the early stages of myocardial infarction may directly cause or precipitate arrhythmias or whether it is merely a coincidental phenomenon reflecting catecholamine stimulation. For these reasons, careful examination should be made of the experimental evidence relating free fatty acid levels to the outcome of acute infarction.

FFA and Experimental Arrhythmias

Kurien et al.[17] injected triglyceride-heparin into closed chest dogs with occlusion of the circumflex coronary artery by an intraarterial balloon; peak rises of free fatty acid levels to 2,000 to 6,000 μEq/liter were followed about 20 minutes later by bursts of ectopic activity including ventricular tachycardia. Opie et al.[18] using an open chest dog preparation with ligation of the anterior descending coronary artery, attempted to repeat the phenomenon without success. However, it may not be the absolute level of free fatty acids that is of decisive importance, but rather the free fatty acid/albumin molar ratio. Circulating free fatty acids are bound to circulating albumin by binding sites with various degrees of affinity for free fatty acids.[19] They are thought to be taken up by the cell in proportion to the circulating concentration, but to a greater degree when the primary albumin-binding sites are exceeded.[20] Thus, the greater the FFA/albumin molar ratio, the greater the possibility that the tight binding sites will be "overoccupied" and that circulating free fatty acid molecules will be held only in loose association with albumin and, therefore, even more readily taken up by the heart.[21] Spector's review[20] stresses the role of the FFA/albumin molar ratio in regulating free fatty acid utilization by tissues.

Rat heart experiments have suggested that a sufficiently high FFA/albumin molar ratio in the perfusion medium can produce arrhythmias even in non-ischemic hearts.[22] The concept that this ratio may be important would explain why Kurien et al.[17] and Oliver,[23] using mongrel dogs, were able to relate ectopic activity to the same level of circulating free fatty acids that did not provoke arrhythmias in the studies of Opie et al.,[18] who used greyhounds with a higher level of serum albumin. However, mongrel dogs were also used by Kostis et al.,[24] who infused triglyceride-heparin to give very high circulating free fatty acid values (and presumably much increased FFA/albumin molar ratios). The ventricular fibrillation threshold was not elevated by elevated free fatty acid levels immediately after coronary arterial ligation or 3 days later. Hence, the relations among circulating free fatty acid values, FFA/albumin molar ratios and experimental arrhythmias are not clear-cut. However, free fatty acids may exert other effects.

FFA and Myocardial Function

Free fatty acids in high concentrations may cause decreased contractility of hypoxic rat papillary muscle[25] or of the flow-limited isolated perfused rat heart.[26] There may be acute dilatation of the underperfused left ventricle,[27] whereas pump failure induced by coronary arterial ligation is lessened by pretreatment with an antilipolytic agent.[28] There appear to be no data showing whether experimental alteration of free fatty acid values in the range actually found in patients with infarction could alter myocardial function.

FFA and Infarct Size

Many diverse factors affect the size of experimental myocardial infarcts.[29] Some agents increasing infarct size (catecholamines and glucagon) raise blood free fatty acid levels and some agents decreasing infarct size (glucose, insulin and potassium, beta adrenergic blocking agents) lower these levels. Nevertheless, direct evidence of an effect of free fatty acids on infarct size has been lacking. Kjekshus and Mjøs[3] substantially raised free fatty acid levels (3,200 μEq/liter) but could find only increased S-T segment elevation after pretreatment of their dogs with antilipolytic agents (see later). It is therefore of interest that release of myocardial enzyme, widely taken to be an index of the severity of experimental myocardial infarction, was several times greater with palmitate in the perfusate than with glucose or glucose plus insulin in isolated rat hearts with coronary arterial ligation.[31] Free fatty acid concentrations and FFA/albumin molar ratios were within the physiologic range. In vivo, free fatty acids can increase circulating insulin values,[32] and this increase could help protect the infarcting tissue from effects of free fatty acids and explain some of the negative findings in Table I.

FFA and Catecholamine Interaction

Catecholamine activity may sensitize the heart to the effects of free fatty acids.[18] In dogs with coronary arterial ligation, circulating levels of free fatty acids were increased by either triglyceride (Intralipid) heparin infusion or catecholamine infusion, and the myocardial oxygen consumption increased; however only during the catecholamine infusion did S-T segment elevation and infarct size increase.[27] Free fatty acid levels of about 1,400 μEq/liter during isoproterenol infusion were associated with greater S-T segment elevation than levels of over 3,000 μEq/liter during triglyceride-heparin infusion.[30] After coronary arterial ligation in the dog, the administration of triglyceride-heparin led to free fatty acid values of nearly 10,000 μEq/liter without effect on the incidence of ectopic beats, but the additional administration of adrenaline at rates of about 1.5 μg/kg per min led to sustained ectopic activity in a small series.[18] In normal dog hearts, the local heat production in the heart increased during both isoproterenol infusion (free fatty acids = 1,800 μEq/liter) and during infusion of triglyceride-heparin (free fatty acids = 3,000 μEq/liter), but more so during the former procedure.[33]

TABLE I

Relation of Free Fatty Acid Concentration and FFA/Albumin Molar Ratios to "Toxic" Effects on Animal Hearts

Authors	Animal Preparation	Circulating FFA Concentration (mM)	Method of Change of FFA	Circulating Albumin Concentration (g/100 ml)	FFA/Albumin Ratio	Effect
Hoak et al.[15£] (1969)	Intact goose	2.7	Glucagon elevation	Unknown	Unknown	Arrhythmias and histologic changes
Kurien et al.[17] (1971)	Closed chest mongrel dog; balloon distension of coronary artery	>3.0	Triglyceride-heparin	Say 2*	5:1–16:1	Ventricular arrhythmias in 60% within 30 minutes
Opie et al.[18] (1971)	Open chest greyhound dog; coronary arterial ligation	>3.0	Triglyceride-heparin	4	3:1–9:1	No arrhythmias in absence of catecholamine infusion. No increase in S-T segment elevation
Henderson et al.[26] (1970)	Perfused rat heart	1.75 linoleate	FFA bound to perfusate albumin	2	6:1	Decreased contractility in face of fixed coronary flow
Henderson et al.[25] (1970)	Rat papillary muscle	1–1.75 linoleate	FFA bound to medium albumin	2	3:1–6:1	Decreased contractility during hypoxia
Opie[159] (1970)	Perfused rat heart	0.5–2.8 octanoate	Octanoate added to perfusate	None	Infinitely high	Heart block and bradycardia
Mjøs[148] (1971)	Mongrel dog	3.0	Triglyceride-heparin	Say 2*	10:1	Increased O_2 uptake
Willebrands et al.[22] (1973)	Perfused rat heart	2–4 oleate; 1–3 palmitate	FFA bound to perfusate albumin	4.5	3:1–6:1 1.5:1–4.5:1	Ventricular arrhythmias in most when FFA/albumin molar ratio exceeded 3:1–5:1
Kjekshus & Mjøs[27] (1972)	Mongrel dog, underperfused left ventricle	3.7	Triglyceride-heparin	Say 2*	12:1	Ventricular dilatation and lactate discharge
Riemersma et al.[58] (1974)	Anesthetized dog; balloon distension of coronary artery	1.5–2.0	Infusion of FFA/albumin	3	4:1–5:1	High incidence rate of side effects (hypotension) in ischemic and in control experiments
Kjekshus & Mjøs[30] (1973)	Mongrel dog; open chest, coronary arterial ligation	3.2	Triglyceride-heparin	Say 2*	10:1	Increased S-T segment elevation after pretreatment with antilipolytic agents
Wildenthal[160] (1973)	Fetal mouse hearts	3.0 oleate or palmitate	Bound to 35% calf serum	Say 1–2	10:1–20:1	Decreases survival in explanted hearts
Kostis et al.[24] (1973)	Closed chest mongrel dog	3.0–5.0	Cotton-seed oil and heparin	Say 2*	10:1–17:1	No change in ventricular fibrillation threshold
Smith & Duce[161] (1974)	Awake dog with coronary arterial ligation and infarction; phase III arrhythmias	1.0 reduced to 0.6	Nicotinic acid analog	Say 2*	3:1 reduced to 2:1	Reduced incidence of phase III ventricular ectopic beats
Opie & Lubbe[162] (1974)	Awake dog with coronary thrombosis and infarction; phase III arrhythmias	1.5–3.0	Triglyceride-heparin	2	5:1–10:1	Ventricular fibrillation not precipitated
de Leiris, et al.[31] (1974)	Isolated perfused working rat heart with coronary arterial ligation	0.5	Added to perfusate	3	1:1	Increased release of lactate dehydrogenase when compared with glucose
Most et al.[165] (1974)	Closed chest pig; balloon distension of coronary artery	About 2.5	Triglyceride-heparin	Say 4 (no data)	4:1	No increase in S-T segment elevation

* Plasma albumin of 2 g/100 ml assumed for mongrel dogs.[23]

Taken together, these experiments suggest that catecholamine activity could sensitize the heart to the effects of elevation of circulating free fatty acid levels. Such sensitization may be related to the capacity of catecholamines to increase myocardial uptake of free fatty acids[34] or to stimulation of endogenous lipolysis in the heart.

FFA and Endogenous Lipolysis in Heart

In the heart, triglyceride can be synthesized from free fatty acids (after activation) and alpha-glycerophosphate, but also broken down by a catecholamine-sensitive lipase to yield tissue free fatty acids and glycerol[35]; this could be termed the "triglyceride-

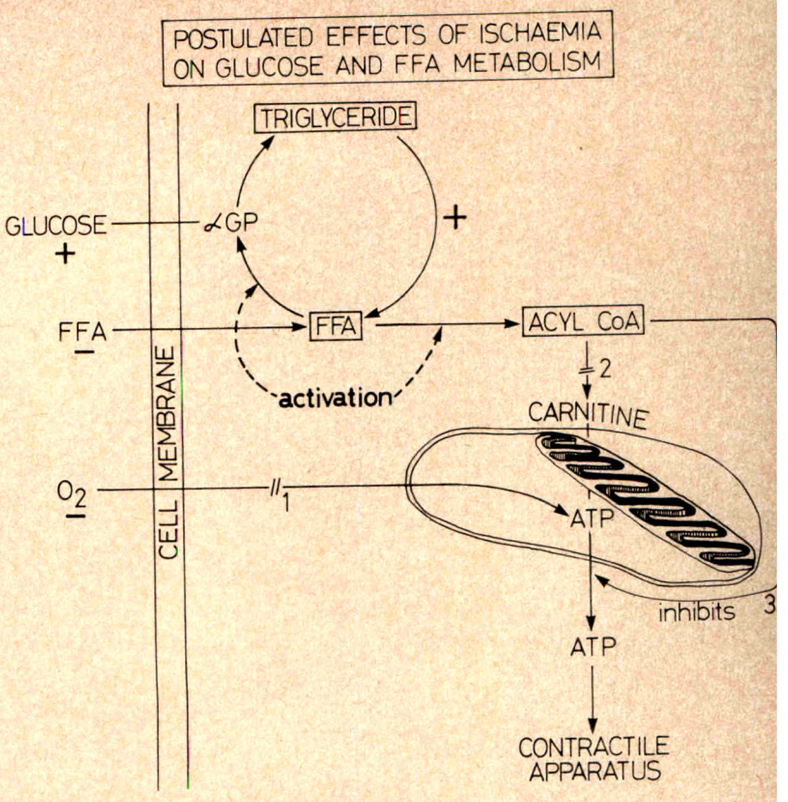

FIGURE 1. Patterns of glycolysis in regional ischemic (infarcting myocardium). Ischemia after coronary arterial ligation causes a stimulation of the uptake of glucose (+) relative to that of free fatty acids (FFA) (−) and decreased uptake of oxygen.[37] Absolute rates of glucose uptake are decreased.[89] Increased breakdown of triglyceride (lipolysis) is accompanied by increased formation of intracellular free fatty acid some of which is released into coronary venous blood[37] and some of which is reesterified with the help of alpha-glycerophosphate (αGP) derived from glycolysis.[38,92] Both breakdown and formation of triglyceride appear to be accelerated,[37–39] but absolute values are unchanged.[42] Decreased uptake of oxygen is associated with decreased delivery of oxygen (1 in schema) to the mitochondria and decreased removal of acyl coenzyme A (CoA), formed from intracellular FFA (2 in schema). Acyl coenzyme A also accumulates because of decreased activity of the carnitine-dependent transferase[52] which normally transfers acyl coenzyme A into the mitochondria. Acyl coenzyme A is thought to inhibit the translocase transferring of adenosine triphosphate (ATP) from mitochondria to the cytoplasmic contractile sites[49,50] (3 in schema), thereby aggravating the ATP deficit in ischemia.

FFA cycle" (Fig. 1). The original Kurien-Oliver hypothesis[36] of free fatty acid toxicity to the heart allowed for catecholamine stimulation causing breakdown of myocardial triglyceride stores (endogenous lipolysis), thereby contributing to the postulated intracellular accumulation of free fatty acids. Measurements of specific activity of plasma free fatty acids entering and leaving the ischemic zone after coronary arterial ligation in the dog suggested a greater efflux from ischemic tissue.[37] In the underperfused left ventricle, there was greater incorporation of labeled circulating free fatty acids into triglyceride and decreased incorporation into tissue free fatty acids, in keeping with an increased tissue content of tissue alpha-glycerophosphate which could enhance rates of esterification.[38,39] Thus, present evidence suggests increased turnover rate of the triglyceride-FFA cycle (Fig. 1) in ischemic tissue.

Indirect evidence for the participation of endogeneous lipolysis in promoting effects of ischemia stems from the data of Kjekshus and Mjøs[30] and Kjekshus,[28] who found that pretreatment by an antilipolytic agent, beta-pyridyl-carbinol, reduced S-T segment elevation after coronary arterial ligation, decreased "pump" failure and sensitized the heart to the effect of exogenous free fatty acids. Stimulation of endogenous lipolysis in the isolated rat heart by epinephrine increased oxygen uptake by about 50 percent.[40]

These data are consistent with but do not directly prove the hypothesis that endogenous lipolysis from net breakdown of myocardial glyceride could contribute to progression of ischemic damage.

Cellular Mechanisms of FFA Effects

Kurien and Oliver[36] postulated that free fatty acids could be related to arrhythmias by accumulation of intracellular free fatty acids with a detergent effect on the cell membranes, thereby promoting egress of potassium ion. Others stressed the possible effect of accumulated free fatty acids on mitochondrial metabolism, with uncoupled respiration[41] or a decrease in the intracellular free calcium ion concentration.[25] However, increased amounts of free fatty acids have not yet been found in ischemic myocardium,[42] although conclusive negative studies would require multiple biopsy sites ranging from infarct center to normal tissue, taken at various periods after the onset of ischemia.

FFA and O_2 uptake of heart: The relation between increased oxygen uptake of the heart and free fatty acids as substrate is open to debate.[43–45] An extreme change from sole use of free fatty acids to sole use of glucose would change the ratio of energy produced (phosphorylation) to oxygen taken up (P/O ratio) from about 2.85 to 3.15, that is, by about 1 percent. Data relating the oxygen uptake of the normal human heart to free fatty acid uptake[46] fall within this prediction. However, in the perfused rat heart free fatty acids as the sole substrate increased the oxygen uptake by about 40 percent,[43] probably as a result of stimulation of nonphosphorylating (oligomycin-insensitive) pathways[47] that account for oxygen uptake but not adenosine triphosphate (ATP) production and are thus measured as an impaired P/O ratio. A conclusive relation between increasing circu

TABLE II

Relation of Free Fatty Acid Concentration and FFA/Albumin Molar Ratios to "Toxic" Effects in Myocardial Infarction in Man

Authors	Clinical Material	FFA Concentration (mM)	Method of Change of FFA	Albumin Concentration (g/100 ml)	FFA/Albumin Ratio	Effects
Oliver et al.[1] (1968)	Patients with acute myocardial infarction	1.2	None	Say 4	2:1	Association with arrhythmias
Gupta et al.[6] (1969)	Patients with acute arrhythmias	1.0	None	Say 4	1.7:2	Association with arrhythmias
Rutenberg et al.[11] (1969)	Patients with acute myocardial infarction		None	Say 4		No association with arrhythmias
Nelson[13] (1970)	Patients on first day of acute myocardial infarction	2.0	Heparin	Say 4	3:1	No arrhythmias precipitated by heparin; no relation of initial FFA and arrhythmias
Russo et al.[16] (1970)	Patients within 48 hours of onset of symptoms of myocardial infarction	1.8	Heparin	Say 4	3:1	No arrhythmias after heparin
Reimann & Schwandt[9] (1971)	Patients with acute myocardial infarction; some treated with heparin	2.0 –3.0	? Heparin (no definite details)	Say 4	3:1 5:1	Serious arrhythmias; ventricular fibrillation
Ravens & Jipp[12] (1972)	Patients within 24 hrs of onset of symptoms	1.6	None	Say 4	3:1	No association between arrhythmias with total FFA concentration; but with relative concentration of linoleate
Prakash et al.[10] (1972)	Patients within 24 hrs of onset of symptoms	1.1	None	Say 4	1.9:1	Correlation between FFA and complications such as left ventricular failure, arrhythmias, shock, death
Hagenfeldt & Wester[15] (1973)	Patients on admission with myocardial infarction	0.8	None	Say 4	1.4:1	No association with arrhythmias
Rowe & Oliver[57] (1974)	Patients within 4 hours of onset of symptoms	1.0–1.5	FFA decreased by nicotinic acid analog	Say 4	1.7:1–3:1	Decreased incidence of ventricular arrhythmias

* In the majority of studies, exact albumin values are not reported and can only be inferred. Our recent measurements on patients show a mean albumin concentration of 4.1 g/100 ml on the 1st day of infarction and 3.8 g/100 ml on the 2nd day.[165]

lating free fatty acid concentrations or increased rates of lipolysis in the ischemic or infarcting heart and decreased mitochondrial metabolism remains to be shown.

FFA and impaired ATP production: Recent data have suggested a second mechanism for free fatty acid "toxicity" involving impaired production of ATP. Intracellular free fatty acids, derived from exogenous free fatty acids or endogenous lipolysis, can readily be activated to long-chain esters[48] (acyl coenzyme A), that are likely to accumulate in ischemia. Acyl coenzyme A accumulation could in turn inhibit the translocase mechanism[49] whereby heart mitochondria take up adenosine diphosphate (ADP) and extrude ATP; the inhibition can be reversed by carnitine.[50] A high concentration of acyl coenzyme A may also contribute to inhibition of the transferase enzyme transporting acyl coenzyme A into mitochondria.[51] Acyl coenzyme A also inhibits the affinity of the mitochondrial phosphorlyation system for added ADP.[49] After coronary arterial ligation, there is depressed activity of the carnitine-dependent mitochondrial enzyme that transfers acyl coenzyme A into the mitochondrial matrix[52]; consequently there could be further accumulation of acyl coenzyme A. The latter could also be produced from triglyceride stores by catecholamine-stimulated lipase activity, thereby providing an explanation of the interaction of catecholamine activity, endogenous lipolysis and exogenous free fatty acids in producing features of lipid "toxicity." It has also been postulated that cardiac accumulation of lipid as triglyceride, as known to occur around the border of infarct tissue and in many pathologic conditions,[35] may be detrimental to the function of the heart.[53]

FFA and action potential of ischemic myocardium: A third possible mechanism for free fatty acid effects relates to recent electrophysiologic evidence suggesting that cytoplasmic ATP produced by glycolysis is required to maintain the duration of the plateau of the action potential.[54,55] In ischemia it is likely that mitochondrial ATP production is decreased; if, in addition, free fatty acids were the predominant exogenous fuel, production of cytoplasmic ATP from glycolysis would become critically decreased and, when the plateau became shortened, ectopic activity might increase. However, data on the effect of free fatty acids on glycolysis and on the action potential of the ischemic myocardium remain to be gathered.

Unphysiologic free fatty acids with unusual chain length and configuration such as erucic acid, derived from rape seed oil, may be more "toxic" to the heart than physiologically occurring free fatty acids,[53] apparently because intracardiac accumulation of deriv-

atives of erucic acid blocks the role of carnitine in oxidation of normal free fatty acids such as palmitate.[56]

Clinical Implications

The free fatty acid concentrations and FFA/albumin molar ratios found to be "toxic" in animal experimental preparations have been compared with those found in patients (Tables I and II). Only in the case of studies relating free fatty acids to infarct size has an effect been found at free fatty acid concentrations and FFA/albumin molar ratios relevant to those reported in patients with acute infarction. An exception in the case of arrhythmias is the study showing a decreased incidence of ventricular ectopic beats in relation to the action of a free fatty acid-reducing agent 48 hours after coronary arterial ligation in the dog; however, we could not promote the development of ventricular fibrillation in a similar preparation with gross elevation of the arterial free fatty acid level by triglyceride-heparin injections. In our experience this phase of arrhythmias (Harris phase III) is harmless in the dog, ends spontaneously and does not resemble the patterns of arrhythmia found in patients with infarction.

FFA, antilipolytic therapy and postinfarction arrhythmias: Critically important observations are now being made by Rowe and Oliver,[57] who have preliminary evidence that antilipolytic therapy can reduce the incidence of ventricular tachycardia in patients, provided that such therapy is started within 5 hours of the onset of symptoms. The plasma free fatty acid values in the studies of Riemersma et al.[58] were reduced from initial levels of only 1,000 to 1,500 μEq/liter; such levels are not arrhythmogenic in animal preparations except when free fatty acids are given directly as FFA-albumin, a preparation that caused profound hypotension and arrhythmias even in the control dogs of Riemersma et al.[58] Hence there is a real possibility that the free fatty acid levels found in man are not by themselves arrhythmogenic. Blood free fatty acid values might be only one of a series of factors facilitating the development of arrhythmias in the infarcting myocardium. Such factors include loss of potassium ion and a high coronary venous concentration of potassium ion,[59] size and location of the infarct,[60] stretch,[61] inhomogeneity of blood flow,[62] catecholamine activity (see later), intracellular acidosis (see later) and variations in circulating levels of potassium, calcium and magnesium ions.[61] Should the clinical observations of Rowe et al.[57] be substantiated, free fatty acids could be considered to be the "last straw" precipitating arrhythmias against a background of complex predisposing factors, among which catecholamine activity could be of major importance (see preceding).

In summary, evidence that free fatty acids in the concentrations found in patients are arrhythmogenic hangs in the balance, and the scales may be tipped by the results of clinical trials now in progress. Evidence that elevation of circulating free fatty acid levels induced by catecholamines can extend the size of experimental infarcts has been obtained with elevated free fatty acid levels relevant to man. To date, all studies with inhibitors of lipolysis have shown an effect in minimizing complications of acute myocardial infarction. Cellular mechanisms for free fatty acid effects may include accumulation of acyl coenzyme A with inhibition of energy transfer from mitochondria and decreased transfer of acyl coenzyme A into mitochondria. At present the balance of arguments suggests that low rather than high free fatty acid concentrations would be more beneficial to patients with acute myocardial infarction.

II. Glucose

Early Observations

The therapeutic use of glucose or glucose-containing carbohydrates in heart disease has been in intermittent favor since the early years of this century when oral intake of cane sugar was recommended on empirical grounds.[63] By 1914, Büdingen[64] provided a rationale based on the role of glucose as myocardial fuel and the association of glycogen depletion with various forms of heart disease. By the early 1930's, the discovery of insulin and the clearer description of angina pectoris and myocardial infarction led to suggestions for the therapeutic use of glucose and insulin in ischemic heart disease.[65] The addition of potassium to glucose and insulin to constitute a therapeutic mixture was a logical step to avoid hypokalemia caused by the intracellular transfer of potassium associated with the use of glucose and insulin.

Glucose-Insulin-Potassium Therapy

Experimental basis: It was Sodi-Pallares et al.[66] who actively advocated the use of glucose-insulin-potassium in ischemic and other forms of heart disease. They argued that potassium loss was an important part of the cellular reaction to ischemia and was associated with "depolarization." Infusion of glucose-insulin-potassium was thought to return potassium ion to the ischemic cells and to help "repolarize" the cells, thereby minimizing an important effect of ischemia and helping to prevent arrhythmias. One review[67] of such therapy for myocardial infarction concluded there was no evidence (1) that the ischemic zone contained fibers that lost only a portion of their potassium, or (2) that infusion of glucose-insulin-potassium could restore potassium in such fibers. However, evidence favoring these hypotheses has been provided by the Sodi-Pallares group,[68–70] who showed that treatment with glucose-insulin-potassium could increase cell or mitochondrial potassium ion in the ischemic zone.[69,70] Regan et al.[59] showed that glucose-insulin-potassium reversed cumulative potassium ion loss from the ischemic myocardium and greatly reduced the incidence of ventricular tachycardia and fibrillation. If potassium loss is a progressive phenomenon[71] and if glucose-insulin-potassium therapy can restore tissue potassium and mitochondria to normal,[69,70] it is difficult to accept Surawicz's alternate postulate[67] that the area depleted

of potassium ion consists of some cells with normal potassium ion and other cells with total loss of potassium ion.

Recent blood flow studies in experimental models of myocardial infarction in the dog[72] and baboon[62] have shown that there is a gradation of blood flow changes, ranging from very low flow rates in the center to relatively high flow rates at the periphery of the infarct zone. Thus the theoretical conditions required by Surawicz[67] for effectiveness of glucose-insulin-potassium in replenishing potassium ion in poorly perfused cells appear to be met.

Clinical data: Why, then, have the concepts of the Sodi-Pallares group not been widely accepted? First, because the patient data have not been published in full and preliminary results have not been conclusive. In their early clinical report Sodi-Pallares et al.[66] found decreased S-T segment elevation in 3 of 10 patients treated with glucose-insulin-potassium but increased S-T elevation in 2 of the group. In another study,[73] glucose-insulin-potassium appeared to abolish residual angina and hasten the evolution of electrocardiographic changes but left unchanged the incidence of arrhythmias and many other complications. Second, some of the published studies tended to carry more theoretical than factual evidence for the use of glucose-insulin-potassium.[74]

Third, theoretical links between potassium ion loss and arrhythmias led to an emphasis on possible relations between glucose-insulin-potassium and the development of arrhythmias. Experimentally, potassium ion loss from the ischemic dog myocardium could be one of the factors precipitating arrhythmias,[59] but reversal of such potassium ion loss in this model could be achieved not only by administration of glucose-insulin-potassium but also by infusion of hypertonic saline and sucrose solutions,[75] thus suggesting that acute increments of extracellular volume could influence myocardial potassium ion transport. It should be noted that readily measurable decrease of tissue potassium ion does not occur for at least 1 to 2 hours after the onset of ischemia.[71] Even coronary local venous potassium ion values need not be closely correlated with postocclusion arrhythmias.[60,76] Thus, no simple relation might be expected between the effects of glucose-insulin-potassium on potassium ion movements and arrhythmias.

Fourth, the conflicting results of many other studies created an air of doubt. Encouraging reports of the use of glucose-insulin-potassium in patients were often open to criticism because of imperfect design of the trials or because of comparison with retrospective data.[77] On the other hand, the negative results of the Medical Research Council trial in Britain[78] were also open to major criticism[79] and the group did not use the doses recommended by Sodi-Pallares et al.[80] Thus it is not surprising that the use of glucose-insulin-potassium for myocardial infarction has not yet become widespread in Anglo-American medical practice.

Recent studies: Four recent developments have rekindled interest in glucose-insulin-potassium infusions. First, well documented experimental studies have shown an effect of such infusions in reducing infarct size (see later). The end point of many previous studies had been arrhythmias, and the possibility of glucose-insulin-potassium altering infarct size was not clinically studied. Second, the clinical studies of Allison et al.[81] in a small group of patients with congestive heart failure have shown that glucose-insulin-potassium can cause ionic shifts of the variety proposed by Sodi-Pallares. Third, theoretical arguments have been advanced that increased provision of glucose might be important for salvaging ischemic tissue.[79,82] Fourth, the current emphasis on very early metabolic therapy for myocardial infarction invalidates the findings in previously reported clinical trials. For example, some of the studies of Sodi-Pallares et al.[73] were started as long as 5 days after admission.

Glucose-Insulin-Potassium and Infarct Size

The work of Sodi-Pallares had already suggested that glucose-insulin-potassium could decrease infarct size because it is known that the degree of S-T elevation after coronary arterial occlusion can be related to the extent of the tissue necrosis. However, the definition of infarct size in those early studies was far from perfect. The recent study of Maroko et al.[83] firmly shows an effect of glucose-insulin-potassium in decreasing infarct size in dogs. In baboons, we found that if glucose-insulin-potassium were given within the 1st hour of coronary arterial ligation, tissue contents of high energy phosphate compounds in the infarcting myocardium were improved.[84] In dogs given glucose-insulin-potassium infusions over 6 hours, there was also increased tissue glycogen in all zones, ATP and creatine phosphate in the infarcted zone, and improved potassium/sodium ion ratio (an index of the degree of necrosis) in the border zone.[85] Thus, animal studies suggest that glucose-insulin-potassium favorably influences the infarct process.

Cellular Mechanisms

Patterns of glycolysis in myocardial ischemia: Several mechanisms, in addition to the Sodi-Pallares concept of replacement of tissue potassium ion, have been suggested to explain the effects of glucose-insulin-potassium on ischemic myocardium. First, increased glycolytic flow could produce increased anaerobic energy. Work with the isolated perfused rat heart[86] has shown that anoxia accelerates glucose transport while the rate of anaerobic glycolysis increases by relief of inhibition of the key glycolytic enzyme phosphofructokinase as a result of changes in the cellular contents of high energy phosphate compounds. In such circumstances, the survival of the heart could be related to the supply of exogenous glucose as fuel.[87] Suggestions of a similar increase in glucose metabolism, relative to that of free fatty acids,

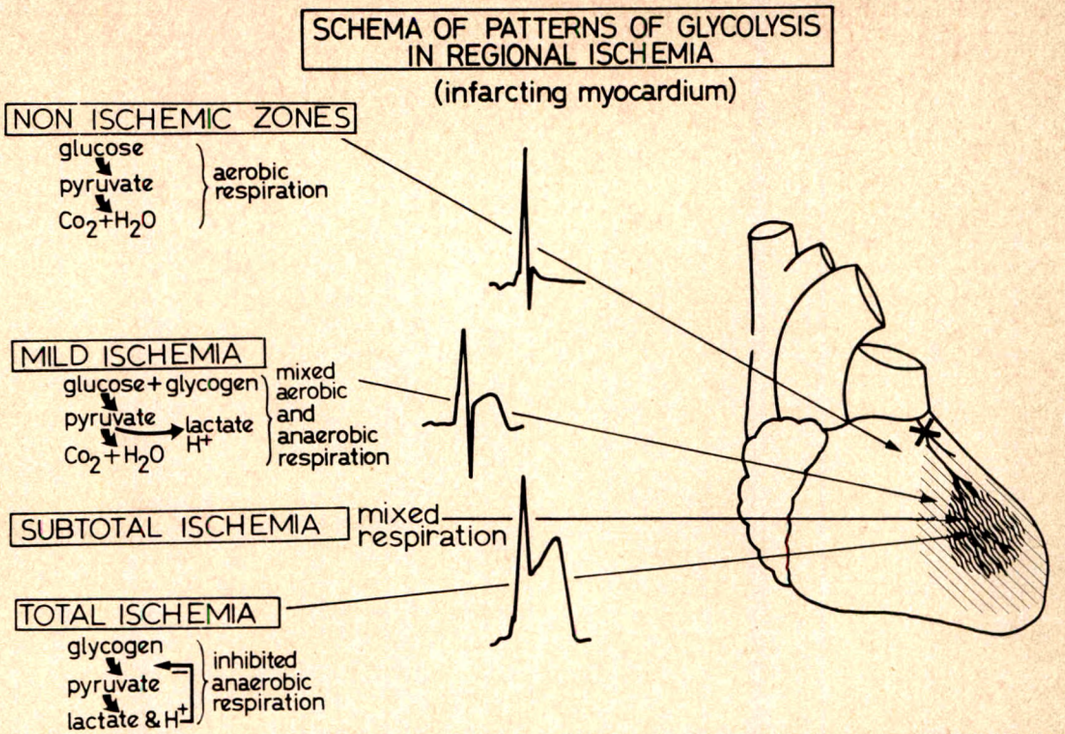

FIGURE 2. Diagram showing the postulated relation between glycolytic flux[156] and regional ischemia after coronary arterial ligation. In nonischemic tissue, with an isoelectric epicardial S-T segment,[83,156] glucose taken up by the heart cells is converted to pyruvate and then to carbon dioxide and water by aerobic respiration; there is no net glycogen breakdown.[35,37] In mild ischemia, with some epicardial S-T segment elevation,[83,157] glucose and glycogen are converted to pyruvate, some of which is oxidized and some of which forms lactate; these are features of mixed anaerobic and aerobic metabolism.[37] It is only in very severely ischemic tissue, with maximal epicardial S-T segment elevation,[83,157] where glucose uptake is minimal and glycogen is the major source of glycolysis[92,156] that pyruvate is entirely converted to lactate. Intracellular acidosis inhibits glycolysis at the level of the enzyme phosphofructokinase[89,90,156]; relatively inhibited anaerobic respiration follows, but glycogen is still broken down. Because collateral blood flow persists for at least 6 hours even in central infarct zones,[156] mixed aerobic and anaerobic metabolism will occur in subtotal ischemia with mitochondrial synthesis the major source of ATP. Zones of different severity of damage after myocardial infarction can be separated by microsphere flow studies,[62] tissue metabolic studies,[84,156] epicardial S-T segment changes,[83,88,157] venous cannulation techniques[37,155] and pathologic criteria. The division of zones in this figure is purely schematic; no direct relation between the degree of S-T segment change and type of metabolism (anaerobic versus aerobic) has yet been shown.

were found after coronary arterial ligation in the dog.[37,88] By analogy it was argued that a therapeutic increase in the supply of glucose could be of critical importance for the survival of those parts of infarcting myocardium perfused by the residual collateral circulation.[79,82] However, there were obvious difficulties in these arguments.

In totally ischemic tissue with no collateral blood flow, it was difficult to visualize how exogenous glucose could contribute to the production of anaerobic energy. In severely ischemic tissue, evidence from both the whole heart ischemic model of Neely's group[89] and from the infarcting dog myocardium[90] suggests an initial rapid acceleration of glycolysis, followed by inhibition at the level of the rate-controlling enzyme phosphofructokinase probably as a result of accumulation of hydrogen ion (Fig. 2). Similar conclusions have been reached during total myocardial ischemia (zero coronary flow).[91] The postulated harmful effects of intracellular acidosis include activation of lysosomes,[92] inhibition of the interaction of calcium with the contractile proteins[93] and increased binding of intracellular free calcium by the sarcoplasmic reticulum and mitochondria.[94] Nevertheless, glycolytic flux from glycogen must continue, as shown by glycogen depletion in central infarction areas. Thus the rate of glycolytic flux in severe ischemia is determined not only by the supply of substrate (glucose versus glycogen) but also by the properties of the enzymes of glycolysis[91] and in particular the response of phosphofructokinase.

In better perfused borderline tissue (Fig. 2) if glucose could reach the infarcting myocardium, then so could oxygen, and the metabolism would be both anaerobic and aerobic in character. In a system designed to give information on those ischemic cells receiving collateral flow and draining into the local vein, coronary arterial ligation decreased free fatty acid uptake relative to that of glucose by ischemic tissue and glycolytic flux remained the major source of energy.[37,88] Thus, both anaerobic and aerobic energy production from glucose were increased in better perfused tissue after coronary arterial ligation. At present there is no conclusive evidence that the addi

tion of glucose-insulin-potassium could further increase glycolytic flux in any part of the ischemic myocardium although arteriovenous differences of glucose across the heart increase after glucose-insulin-potassium.[85] However, there is evidence that glucose-insulin-potassium can spare glycogen in developing infarction,[84,85] thereby possibly preventing potassium loss and protecting against anoxia.

Glucose-insulin-potassium and lipid metabolism: A second possible mechanism of action of glucose-insulin-potassium metabolism could be interaction with lipid metabolism. Because glucose given intravenously or orally reduces circulating free fatty acids in patients with acute myocardial infarction,[5,6] it could be held that glucose-insulin-potassium acts on adipose tissue to inhibit lipolysis and to reduce circulating free fatty acid concentrations from "toxic" levels; the concept of free fatty acid "toxicity" has already been discussed. Acting at a cellular level, glucose-insulin-potassium might promote glycolysis and provide an increased supply of alpha-glycerophosphate[39,92] for reesterification of intracellular free fatty acids, thus removing the postulated free fatty acid or acyl coenzyme A accumulation in ischemia (Fig. 1).

Hyperglycemia and blood osmolarity: Third, in several of the reported studies, hyperglycemia occurred and increased blood osmolarity was probable; it should be noted that the use of mannitol also appeared to diminish the consequences of myocardial ischemia.[95,96] But the increase in osmolarity required for such effects may be more than 60 mOsm according to studies on hypoxic papillary muscle.[97]

Elevation of plasma volume and nonischemic tissue: Fourth, Burke et al.[75] suggested that glucose and nonglucose infusions could have as a common mechanism of action an acute elevation of plasma volume with an inotropic left ventricular response. Fifth, glucose-insulin-potassium may act by altering metabolism in noninfarcting relatively well perfused myocardium,[84] which is known to undergo metabolic changes during acute coronary arterial ligation.[98]

Insulin effects: Sixth, glucose-insulin-potassium may act in part by increased provision of insulin. In acute myocardial infarction there is insulin resistance and a circulating insulin level inappropriately low in relation to the elevated blood sugar.[99,100] Hence, if glucose were to act by crossing the cell membrane, it would seem logical to add insulin. However, insulin may have effects independent of glucose transport, such as enhanced membrane polarization in skeletal muscle,[101] inhibition of lysosomal activity in hypoxic heart tissue,[102] and (in massive doses) inhibition of postocclusion arrhythmias.[103] In ischemic rat hearts perfused with glucose, insulin may enhance the rate of lactate accumulation in ischemic tissue,[89] suggesting intracellular acidosis. It is not known whether cellular metabolism improves as a result of concomitant glycolytic adenosine triphosphate production or deteriorates from the presumed acidosis, but studies in dog hearts infused with glucose-insulin-potassium after coronary aterial ligation show metabolic improvement rather than deterioration.[85] Our data also show a clear effect of glucose and insulin in limiting release of lactate dehydrogenase from the isolated rat heart perfused with fatty acid after ligation of the left coronary artery[31]; there was also an effect of insulin when the perfusate contained only free fatty acids as substrate.

Clinical implications: Much more needs to be known about glucose-insulin-potassium and the separate contributions of glucose, insulin and potassium to the effect on the infarcting myocardium. The studies of Maroko et al.[83] show that glucose alone was nearly as effective as glucose, insulin and potassium in reducing infarct size after coronary artery ligation in dogs, thus suggesting that glucose is the most important component in glucose-insulin-potassium therapy. Furthermore, Regan et al.[59] showed that insulin only transferred potassium ion into the ischemic zone in the presence of hyperglycemia. The findings of beneficial effects on infarct size in the dog,[83,85] increased high energy phosphate compounds in the baboon[84] and decreased release of enzyme in the isolated rat heart[31] (all with coronary arterial ligation), together with the earlier data of Sodi-Pallares et al., all suggest that it is worth persevering with studies to elucidate the possible mechanism of the beneficial effect of glucose-insulin-potassium in greater detail with the aim of providing a rational rather than empirical form of therapy. Further clinical trials, with infarct size as an end point, are also required.

III. Catecholamines

Catecholamine Metabolism in Acute Myocardial Infarction

Psychologic stress: The patient with the sudden onset of chest pain caused by acute myocardial infarction suffers from both physical and psychologic distress. One may expect all the metabolic derangements characteristic of acute psychologic stress,[104] including an acute release of catecholamines. In healthy people urinary or blood catecholamine values can change quickly and markedly in response to stress. In sexual arousal or in physical stress such as simulated battle conditions[104] urinary catecholamine secretion rates can approach those found in milder cases of myocardial infarction. Immediately after the severe emotional stress of racing-car driving,[105] plasma concentrations of both noradrenaline and adrenaline (mean values 3.5 and 0.6 μg/liter, respectively) equal or exceed those found in the blood of patients who have had a myocardial infarction. Measurements of plasma and urinary catecholamines suggest greatly increased catecholamine secretion rates in the first 24 hours after the onset of chest pain,[3,6,106] with the greatest rate of rise of plasma catecholamines in the 1st hour of the onset of myocardial infarction.[100] An association between psychologic stress and blood and urinary catecholamine concentration is suggested by the increased urinary values found when patients are

transferred from coronary care units to other wards.[107,108]

Free fatty acids and catecholamine levels: It has been suggested that the blood level of noradrenaline plays a major role in the regulation of the circulating free fatty acid concentrations and that emotional stimuli increase noradrenaline rather than adrenaline values.[109] In contrast, exercise-induced elevation of both noradrenaline and adrenaline is postulated to be less harmful to the heart because exercise utilizes the circulating free fatty acids and decreases the concentration, whereas emotion elevates these values.[109] However, a relation between circulating adrenaline and free fatty acid values is also reported.[110] Urinary catecholamine values (which are considerably easier to measure than blood catecholamine values) show a better relation between circulating free fatty acids and adrenaline than noradrenaline values after myocardial infarction.[6] Infusion of adrenaline is followed by a rise in plasma free fatty acid values closely corresponding to blood adrenaline concentrations, but with noradrenaline infusions the relation to the rise in free fatty acids is not so clear.[106]

Parasympathetic nervous system: On clinical grounds, Webb et al.[111] recently suggested a preponderance of parasympathetic discharge in about two thirds of patients seen very early after the onset of infarction. Little is known about the role of the parasympathetic nervous system in precipitating arrhythmias but bradycardia in response to vagal stimulation may facilitate the development of ectopic beats[112] and fatal arrhythmias.[113,114] Nevertheless, the clinical finding of an apparently predominant parasympathetic reaction does not exclude increased catecholamine secretion rates.[3]

Catecholamines and Arrhythmias

The occurrence of serious arrhythmias has been linked with increased urinary catecholamine concentrations in patients with acute myocardial infarction.[6,115–117] In patients with well maintained renal function, there is a good relation between urinary and blood catecholamine concentrations[106]; hence, there is also a relation between blood catecholamine concentrations and arrhythmias. Valori et al.[110] have also shown that peaks in values of both noradrenaline and adrenaline concentrations (and of free fatty acids) could be related to the onset of arrhythmias, and Siggers et al.[108] found a relation between ventricular ectopic beats and peak plasma adrenaline values. One report[118] has suggested that total catecholamine concentrations in the blood do not have a close temporal relation to early arrhythmias. However, in that report, adrenaline only constituted about 1/30 of the total measured blood catecholamines, which is a much lower fraction than that found in many other studies. Also, using a double isotope technique, Siggers et al.[108] found blood adrenaline values to be considerably higher and about one half or more of the noradrenaline values; Valori et al.[110] used a modified and very sensitive fluorometric technique and found that plasma adrenaline concentrations were about one third those of noradrenaline. Such large discrepancies in blood adrenaline values in myocardial infarction indicate that present measurements of blood adrenaline concentrations are open to question. Nevertheless, the overall data suggest a real relation between catecholamine concentrations and arrhythmias.

The catecholamine secretion rate, rather than the blood or urinary concentration, has been related to early arrhythmias in the dog by Ceremuzynski et al.[119] Videbaek et al.[118] argue that their estimated secretion rate of catecholamines was only 0.3 μg/kg per min and that this is "very unlikely" to produce arrhythmias in experimental myocardial infarction. However, Ceremuzynski et al.[119] found catecholamine secretion rates of this order to be associated with arrhythmias in dogs.

There can be no doubt that catecholamine infusions in sufficient doses can precipitate arrhythmias in experimental myocardial infarction. Even 4 days after coronary arterial ligation, catecholamine administration provoked ectopic activity.[113] A critical point is whether catecholamines act largely through elevation of circulating free fatty acids or by stimulation of myocardial lipolysis or by mechanisms not involving lipid metabolism (see later).

Catecholamines and Infarct Size

The production of ischemia by coronary arterial occlusion leads to potassium and inorganic phosphate loss into coronary venous blood, but the infusion of low subpressor doses of noradrenaline can return potassium and phosphate levels to normal.[120] Our experiments showed that after occlusion of a very small branch of the coronary artery, there was a detectable rise in venous potassium and phosphate concentrations, but minimal electrocardiographic changes; then adrenaline was infused at rates similar to the secretion rates found in dogs with much larger infarcts,[119,121] whereupon there was a prompt increase in the epicardial S-T segment elevation (in confirmation of the findings of Raab et al.[122]) and further potassium and phosphate loss.[123] The infusion of catecholamines produced a metabolic result similar to that of ligation of a larger artery. Infused adrenaline may harm the noninfarcted myocardium, as evidenced by depletion of enzymes.[124] Further evidence for a role of catecholamines in the determination of the outcome of experimental myocardial infarction is that when propranolol is given to dogs after coronary arterial ligation, there is decreased S-T segment elevation[29] and decreased tissue necrosis.[125] Propranolol (0.1 mg/kg) given intravenously to patients with recent acute myocardial infarction uncomplicated by left ventricular failure also decreased metabolic damage as shown by improved lactate extraction.[126]

In even larger doses, catecholamines may (1) produce large scale infarct-like necroses even in the total

absence of coronary arterial narrowing, as shown by Rona et al.[127]; (2) cause uncoupling of mitochondrial respiration[128]; and (3) give rise to "oxygen-wastage."[129] Catecholamine-induced cardiac necrosis in rats is in part prevented by treatment with an antilipolytic agent,[130] thus suggesting that stimulation of cardiac lipolysis[40] or increased uptake of circulating free fatty acids, or both, could play a role in the genesis of necrosis.

These data suggest that dose effects may be important in the metabolic response of the ischemic area to catecholamines in dogs. In addition, epicardial S-T segment elevation after coronary arterial ligation was also decreased by smaller doses of catecholamine (levarterenol, 0.1–0.2 μg/kg per min, and epinephrine, 0.5 μg/kg intravenously),[131] while S-T elevation was increased by larger doses (norepinephrine 5–25 μg/kg intravenously).[122]

Determinants of catecholamine effects in infarction: There are several other important determinants of catecholamine effects in experimental infarction. First, the functional status of the left ventricle is relevant because small doses of isoproterenol could sometimes produce a positive inotropic effect without increasing the severity of ischemic damage in the dilated failing heart.[132] Second, the relative degrees of alpha and beta adrenergic stimulation may be important.[133] Alpha adrenergic stimulation causes increased systemic hypertension, which could have both beneficial effects on infarct size (increased coronary perfusion pressure) and harmful effects (increased oxygen demand from increased afterload). Experimentally, methoxamine given to dogs with apparently similar infarcts increased infarct size in one set of experiments[29] and decreased it in another.[133] The improvement found in hypertensive patients with acute myocardial infarction after the use of phentolamine[134] indicates that alpha adrenergic stimulation can have overall harmful effects in certain patients with myocardial infarction. Beta adrenergic stimulation may increase the oxygen demand of the ischemic zone, decrease coronary perfusion pressure and increase the heart rate; hence, isoproterenol (0.25 to 0.50 μg/kg per min) increased infarct size in dogs.[29,133] On the other hand, mixed alpha and beta adrenergic stimulation by norepinephrine (4 μg/min) increased coronary perfusion pressure, decreased heart rate and caused a sustained increase in the contractility of the border zone, suggesting that the increased oxygen demand was balanced by an increased oxygen supply.[133] In the presence of global left ventricular ischemia, norepinephrine (0.4 μg/kg per min) increased contractility, coronary perfusion and ventricular function.[135]

Third, catecholamine effects on heart rate also need consideration. In patients, the optimal heart rate after acute myocardial infarction may be between 60 and 80 beats/min,[114] and reduction of the heart rate by beta adrenergic blockade is associated with decreased S-T segment displacement.[136] Tachycardia can worsen the development of experimental ischemia[137] and may even increase infarct size 14 to 72 hours after the constriction of a coronary artery in dogs.[138] To separate the chronotropic and inotropic effects of catecholamines, Kannengiesser et al.[139] used an isolated rat heart model of myocardial infarction to show that an increased heart rate induced by pacing or isoproterenol led to acute cardiac failure; at a constant and paced heart rate, the initial inotropic stimulus of isoproterenol was also followed by cardiac failure; thus, both inotropic and chronotropic effects increased myocardial damage.

Finally, the degree of expression of catecholamine activity may be masked by simultaneous reflex vagal activity.[140]

Cellular Mechanisms for Catecholamine Effect

Catecholamine-induced worsening of ischemia is thought to result from an increasing disparity between the oxygen supply and demand of the ischemic tissue. In normally oxygenated hearts catecholamine stimulation leads to increased breakdown of glycogen and endogenous lipid. In the ischemic myocardium products of glycolysis and lipolysis (hydrogen ions and acyl coenzyme A) which are normally removed by oxidative metabolism would tend to accumulate. As already reviewed, both hydrogen ion and acyl coenzyme A accumulation are harmful to ischemic tissue. Catecholamines may impair the residual oxidative metabolism of ischemic tissue by several mechanisms, including an inotropic effect of catecholamines on the ischemic myocardium in the face of unchanged oxygen delivery, and impaired mitochondrial function with a decreased phosphorylation-oxidative ratio.[128] In addition, increased entry of calcium ions, a consequence of catecholamine stimulation of the heart cell, is thought to be an important factor in the production of ischemic necrosis.[141] These effects could explain deterioration of infarcting and noninfarcting myocardium when catecholamines in sufficient doses reach the myocardial cell. The source of such catecholamines could be either increased circulating catecholamines or catecholamines released from the ischemic tissue.[142]

Possible links between catecholamine activity and arrhythmias are: (1) stimulation of lipolysis[36]; (2) increased potassium loss (see earlier); (3) increased peripheral vascular resistance with systemic hypertension[17,113]; and (4) slowing of conduction resulting from catecholamine-associated depolarizations induced by the inward calcium current.[143] The arrhythmogenic action of catecholamines may be multifactorial in origin.

Comparison with Other Inotropic Agents

While it would seem simplest to assume that all inotropic agents increase contractile state and myocardial oxygen uptake to the same degree,[144] the work of Mjøs et al.[145] has suggested that at least part of the "oxygen-wastage" effect of catecholamines might be due to their considerable effect in mobilizing free fatty acids. Mjøs[146] has produced suggestive evidence that the elevated circulating free fatty acid concentrations associated with increased circulating cate-

cholamines might increase the myocardial oxygen demand more than calcium gluconate. In experimental myocardial infarction,[30] the infusion of catecholamines gave rise to greater S-T segment elevation when circulating free fatty acid levels were allowed to rise than when an antilipolytic agent was administered. Thus, free fatty acid-mobilizing agents such as catecholamines and dopamine[147] may further compromise the utilization of oxygen by the heart, in a way in which other inotropic agents such as calcium or glucagon do not.[145,148]

Clinical Implications

Because catecholamines administered as inotropic agents may buy increased myocardial performance at inflationary prices (increased metabolic demand) and ultimate functional deterioration,[139] it could be argued that catecholamines should be used as inotropic agents only after careful consideration and for certain specific circumstances. A case has been made for the therapy of cardiogenic shock with noradrenaline[149] or both noradrenaline and small doses of isoproterenol to achieve optimal alpha and beta receptor stimulation.[150] Pure beta receptor stimulation by isoproterenol increased infarct size in dogs, whereas combined alpha and beta receptor stimulation by norepinephrine decreased infarct size.[133] The simultaneous administration of an antilipolytic agent should decrease the potential damaging effects of catecholamines and would warrant exploration.

Guides to inotropic therapy in myocardial infarction: In a given patient requiring an inotropic agent it might not be obvious whether the administration of catecholamines would be beneficial. There are several methods of monitoring the potential effects. First, sequential measurement of precordial S-T segment changes are possible in patients with anterior myocardial infarction. Lamont and Posel[151] have already used S-T segment changes as a guide to the dosage of isoproterenol in patients, whereas Pelides et al.[152] have shown decreased precordial S-T segment elevation in patients with acute infarction given beta blocking drugs even though the studies were undertaken 5 to 72 hours (mean 33 hours) after the onset of chest pain. Maroko and Braunwald[82] in their recent thorough review of the application of measurements of S-T segment changes to the assessment of experimental infarct size included a preliminary report on the use in man. Second, from sequential blood enzyme changes, it might be possible to project the natural history of myocardial infarction from early values by the technique developed by Roberts et al.[153] in dogs; thus an increased rate of rise of blood enzymes such as the MB isoenzyme of creatine phosphokinase[154] may indicate increasing myocardial damage in patients. Third, coronary sinus catheterization has already been successfully undertaken even in patients with cardiogenic shock[149] and allows monitoring of arteriovenous differences of potassium ion, lactate and inorganic phosphate across the heart. An increased venous discharge of these ions would probably indicate extension of myocardial ischemia, although the problem of admixture of nonischemic and ischemic blood into the coronary sinus would need consideration.[155]

Conclusions

Free fatty acid values: In the early stages of acute myocardial infarction, metabolic and pharmacologic manipulation in animals has shown that the amount of ensuing ischemic damage and infarction can be modulated. A critical assessment is made of the hypothesis that elevated free fatty acid concentrations found in patients with acute myocardial infarction may be "toxic" and arrhythmogenic. Consideration of the free fatty acid concentrations and the FFA/albumin ratios that adversely affect the heart in animal experiments suggests that circulating free fatty acid concentrations actually found could only rarely be directly arrhythmogenic in infarction. However, there is evidence that free fatty acids could act synergistically with increased catecholamine concentrations to harm the ischemic heart and to promote arrhythmias, and that free fatty acids could extend the infarct size after experimental myocardial infarction. It is concluded that the balance of evidence suggests a "toxic" role for free fatty acids if present in sufficiently high circulating concentrations. One method of decreasing circulating free fatty acid levels is by the use of glucose-insulin-potassium therapy.

Glucose-insulin-potassium therapy: This modality was introduced with the aim of "repolarizing" ischemic tissue, which led to an emphasis on a possible antiarrhythmic effect. Experimental and clinical evidence for the use of glucose-insulin-potassium as antiarrhythmic therapy is inconclusive, but there is strong experimental evidence that it can reduce infarct size. The mechanisms involved are ill understood, and may include increased entry of potassium ion into ischemic tissue, as originally proposed by Sodi-Pallares, increased cardiac glycogen and perhaps enhanced rates of anaerobic adenosine triphosphate production; a direct effect of insulin cannot be excluded.[156] It is suggested that infarct size be the future end point of clinical trials involving glucose-insulin-potassium.

Catecholamines: These naturally occurring inotropic agents are found in increased amounts after acute myocardial infarction in man. Both clinical and experimental data show a role for catecholamine activity in the initiation or arrhythmias. Dose effects and the type of catecholamine may determine the response of the ischemic myocardium to infused catecholamines; very small doses tend to reverse and large doses to aggravate ischemic changes. In addition, hemodynamic factors such as the size of the heart and magnitude of the afterload and aortic and coronary perfusion pressure are critical in the response of the infarcted heart to catecholamines. The relations among the metabolism of catecholamines, free fatty acids and glucose and the outcome of myocardial infarction have been delineated in experimental animals but the application to patients is under investigation in several centers.[57,82,126,134,149]

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Carrel and Tuffier (1914) on Experimental Surgery of the Cardiac Orifices

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In 1913, only a few years after the experiments of MacCallum[1] and those of Cushing and Branch,[2] Alexis Carrel, the experimental physiologist, was joined at the Rockefeller Institute by the great French surgeon Theodore Tuffier (1857–1929). Their collaborative experiments on the heart valves of the dog were presented before the Academy of Medicine in Paris in a brief note,[3] which was discussed in this Journal in 1969.[4] The researches of Carrel and Tuffier also formed the basis for a longer essay, which the experimenters titled "Chirurgie des Orifices du Coeur" and published in the *Presse Médicale* in 1914. The discussions in this essay tell us much about the embryonic art of cardiac surgery.

Excerpts from Carrel and Tuffier*

To ascertain whether some cardiacs may benefit from surgery, this is the question that we wish to examine. In order to answer it we must inquire into (1) pathological anatomy and clinical medicine, and (2) experimentation and operative technique.

Does pathological anatomy show us valvular lesions capable of amelioration by a mechanical act? With respect to this question it is necessary to take into account some causes of error. Autopsy specimens show only ultimate lesions, maxima, which the [surgical] operator does not encounter in such a marked degree. Processes secondary to a cardiac lesion do not produce counterindications to operation, since these secondary lesions will be prevented by an early operation that removes the primary obstacle. The marvellous anatomical collections of cardiac lesions assembled and preserved by Dr. [Emanuel] Libman at the Mount Sinai Hospital of New York, the beautiful specimens in Letulle's special collection, those of Vaquez and P. Marie at the Faculty in Paris—such are the materials that we have consulted.

The examination must bear upon: (1) the lesion at the orifice, (2) the condition of the heart, (3) the condition of the vessels. These three components must be considered in judging the possibility or the effectiveness of an operation on the heart. From our investigation it is apparent that, under sharply defined conditions, pure mitral stenosis and some stenoses of the pulmonary artery may benefit from operation.

Anatomically, pure mitral stenosis is a lesion limited to the valve; for a long time the heart muscle and the peripheral circulation remain unharmed. The free border of the valve alone is affected, the valves themselves remain smooth and supple. It is moreover the lesion that has most vividly impressed physicians, and Brunton* at the autopsy of a young girl in whom he found the mitral orifice alone to be stenotic, had the impression that incision of the stricture would remove the obstacle, which was the only barrier to normal circulation. Bouillaud's comparison of pure mitral stenosis and palpebral stenosis should be preserved if surgical treatment is to be considered.

Aortic stenosis can occur in three regions—valvular, supra-aortic, and subaortic. The subaortic variety, described by Vulpian in 1868, is inaccessible to surgical treatment by reason of its location below the annulus fibrosus at the level of the mitral-aortic channel. Supra-aortic stenosis is rare. The truly surgical variety is valvular stenosis. It is characterized by adherence between the free edges of the valves, with thickening and deformation of their edges. It is a simple ring with indurated margins. A picture by Letulle† portrays it exactly, and the lumen of the vessel reduced to the diameter of a pencil is the emblem of all the mechanical disturbances of which the pathologic process consists. Exceptionally the lesion affects the fibrous circle by which the valve is implanted on the aortic wall . . . .

Stenoses of the pulmonary artery have the same anatomical traits. The infra- and supra-orificial varieties are very rare and need not detain us. Valvular stenosis is the most frequent. The fibrous arch of insertion is intact. Fusion of the margins of the valve produces a sort of diaphragm, convex toward the pulmonary artery; its more or less narrow central cleft is capable of being enlarged.

Paradoxically, the pulmonary artery is dilated beyond the stenosis, through loss of the elasticity of its walls. In young patients stenosis of the pulmonary artery can be pure, unaccompanied by any alteration of the myocardium and any congenital malformation at other orifices; this condition is eminently favorable for mechanical treatment.

According to Schepelmann‡ congenital tricuspid stenoses, which have the same characteristics, would be especially suitable for surgical intervention, since the heart is intact.

From the fact that a lesion at an orifice presents itself under anatomical conditions that make an attack possible,

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* Lauder Brunton.—"Preliminary note on the possibility of treating mitral stenosis by surgical methods." *The Lancet,* 1902, t. 1, p. 362.

† *Presse Médicale,* no. 99, December 1913.

‡ Schepelmann.—*Langenbecks Archiv,* 1912, t. XCVII, p. 739; *Deutsche Zeitschr. f. Chir.,* t. CXX, Heft 4.

and from the fact that the state of the myocardium and the vessels shows that the attack is well grounded, it does not necessarily follow that an operation is indicated. The lesion by its persistence or progress must cause disturbances that are serious or will be fatal in the near future. This is the indication for a surgical attempt.

Now, from all our reading, from all our inquiry among internist colleagues, it is concluded that this indication is rare, but that it presents itself distinctly in certain cases. In pure mitral stenosis cases similar to those of Brunton (*loc. citat.*) are encountered: a young patient, stenotic lesion at the orifice with progressive evolution revealed by functional disturbances, intact myocardium, and yet a fatal outcome. No medical measure could stop its progress.

Certain aortic stenoses which progress slowly but continuously, with hypertrophy of the left ventricle, can also be regarded as mechanical lesions suitable for mechanical treatment, i.e. for enlargement of the valvular chink.

Stenoses of the pulmonary artery, when they are isolated, independent of other cardiac malformations, almost always end fatally and within a period resembling that of pulmonary tuberculosis.

In this review there is no discussion of orificial insufficiency. In the opinion of all our colleagues, these insufficiencies usually develop slowly, are readily compensated, and are compatible with long life. We wish to remark on this fact and to emphasize the difference between the disturbances caused by stenosis at an orifice and those caused by insufficiency. Our surgical treatment will consist exactly of transforming serious stenoses into relatively mild insufficiencies . . . .

[Carrel and Tuffier then discuss surgical dangers: accidental injury of the coronary arteries, entry of air into the heart and vessels, and thrombosis. They enumerate danger zones and "manageable" zones in the heart, and consider the length of time that various major vessels may be compressed. They then describe their operative technique.]

For stenosis at an orifice we have three operations: internal valvulotomy, which is analogous to internal urethrotomy; external valvulotomy, including cardiotomy, analogous to external urethrotomy; and auriculoventricular or arterioventricular anastomosis, which consists of using a bypass channel to establish communication between the segment above the stenosis and the segment below it.

Internal valvulotomy—section of the valve from within outward—can be done in two ways: by an incision in the vicinity of the stenosis or by a remote incision. If the case is one of mitral stenosis, the stenotic valvular diaphragm can be reached by two routes: indirectly by way of the carotid or directly across the ventricular wall. The first has been followed by Rosenbach . . ., who cut the valves by means of a very long instrument, a sort of sound equipped with a covered blade at its end, the Klebs valvulotome. Rihl* used an analogous procedure when he destroyed the tricuspid valves by means of a long sound introduced into the right heart by way of the jugular vein.

The mitral or tricuspid valves can be reached more directly by using an artificial wound, auricular or ventricular, i.e. by cardiotomy. Since haemorrhage from the friable auricle is harder to stop, the ventricular route must be preferred. Brunton, apparently the first experimenter on this subject, introduced a thin but strong instrument, a tenotome, through a very small wound in the ventricle. With this he sectioned the greatest part of the valve. Cushing* in 1908 used the same technique. According to him the operation requires extensive practice on the cadaver in order to familiarize the surgeon not only with the anatomical location of the valves but also with the special sensation produced by cutting the valve or the chordae tendineae. In his experiments he used MacCallum's hook. Of 25 animals operated on by Henry and Heuer (*in* Cushing and Branch), several of which had valvular lesions analogous to those in man, 11 recovered and were able to compensate rapidly for the experimental lesion. Cushing concluded that the transformation of a stenotic orifice into an insufficient orifice was a considerable amelioration, and that an operation of this kind could be attempted successfully in man . . . . Schepelmann† cut the chordae tendineae of the anterior and posterior papillary muscles by means of a knobbed chordotome introduced via a wound in the anterior ventricular wall. When the knobbed knife reaches the chordae the sharpened part of the instrument is put against them and by a barely perceptible jolt the tendons alone are cut. During this blind operation the danger zones of the heart can be injured. Therefore it seems to me preferable to excise the valves through a larger incision in the cardiac wall under direct vision.

If the valvular diaphragm is simply cut, without a portion being resected, it is necessary to fix one of the lateral components to the ventricular wall with a silk thread in order to prevent coalescence and secondary fusion of their edges; in the same way the eyelids are immobilized after they have been liberated by tarsorrhaphy.

Carrel believes that he can dilate stenotic valves by forcing them with a finger introduced into the cavity of the heart. In a case of aortic stenosis in my clientele in which I operated last year in company with Carrel, I sought to obtain this result. I continue to see the patient, who feels improved . . . .

External valvulotomy, which we shall now consider, is based on the opposite principle, incision from outside in. The aortic orifice and the valve are split at the same time.

This direct section of the valve must be done in a very precise way, because the cardiac region which surrounds the aorta and the pulmonary artery is especially sensitive and it readily gives rise to reflexes. It is essential to withdraw as far as possible from the neighborhood of the coronaries, although they arise far enough away for one to pass between them on the anterior surface of the aorta.

Section of the valves is a blind procedure which cannot be controlled, but is it not possible to put a patch over the aorta like a flap or a half-flap? A piece of femoral artery or vein kept in cold storage can be used. It is also possible to use the patient's saphenous vein, which is sewn to the arterial wall on three of its sides; only the fourth side is left free and is allowed to gape open. Beneath this, in the opening between it and the base of the vessel, a knobbed bistouri is inserted and the valve orifice is split. Then in order to close the wound it is sufficient to sew the last side of flap; this takes 10 to 15 seconds. When the dimensions of the piece and its sutures have been calculated correctly, this "patching" makes it possible to enlarge the opening. Thrombosis need not be feared, since the patch has its endothelium . . . .

* Rihl.—"Experimentelle Trikuspide Insufficienz." *Zeitschr. f. experim. Pathol. und Therapie,* t. VI, p. 616.

* Cushing and Branch.—"Experimental and clinical notes on chronic valvular lesions in the dog and their possible relation to a future surgery of the cardiac valves." *Journ. of Medical Research,* 1908, vol. 12, pp. 471–486.

† Schepelmann.—*Arch. f. klin. Chir.* 1912, t. LXXXXVII p. 739.

[The authors describe their surgical techniques. The paper ends with brief reports of six operations in dogs.]

Experiment 1. *Incision and suture of the ascending aorta.* White female dog of medium size and bad general constitution, no. 3232, October 21, 1913. Etherized by the Meltzer-Auer method . . . The ascending aorta was opened by a longitudinal incision about 2½ cm. long, made in the anterior aspect of the aorta and extending to the base of the heart. Abundant haemorrhage. The finger was thrust into the wound and the vessels were compressed digitally above the wound. Continuous suture of the aortic incision. The heart was beating gently and irregularly. The clamps were removed. The circulation was normal. After a few minutes the heart was regular again. The pericardium was closed. The thoracic cavity was sutured . . . On November 3 the animal was in good condition . . .

Experiment 2. *Patching of the pulmonary artery* . . . October 23, 1913 . . . The base of the pulmonary artery was explored very easily. A piece of aorta obtained from a human fetus and preserved for 24 hours in the icebox was placed over the anterior surface of the artery and over the ventricle. The superior and lateral part of this piece of artery was fixed to the wall of the pulmonary artery by continuous sutures. Then the pedicle of heart was grasped in an elastic clamp, a thin bistouri was introduced under the patch, between it and the wall of the pulmonary artery, which was cut longitudinally. The incision was too high and too short. Then the inferior part of the patch was sutured to the wall of the artery. Thus it was fixed on all sides . . . The next day the animal was walking in the room. On November 3 it was in normal condition . . .

Experiment 4. *Patching of pulmonary artery. Death from wound of a coronary artery* . . . Incision of the pericardium and exploration of the pulmonary artery. On the axial part of the artery a large piece of aorta was placed; this had been taken from another dog and kept in the icebox for a day. The uppermost part and the two sides of this fragment were fixed to the pulmonary artery by a continuous suture. The pedicle of the heart was grasped in a clamp. The tip of a fine pair of scissors was introduced under the patch and the wall of the pulmonary artery was cut at the level of the base of the pulmonic valve . . .

Comment on Carrel and Tuffier

In 1914 the paper by Carrel and Tuffier must have seemed thrilling and almost incredible. Even at a distance of more than 60 years it conveys an impression of boldness and novelty.

As a footnote indicates, the work was done at the Rockefeller Institute, with which Carrel had been connected since 1909. The experimenters were helped by having had access to collections of gross specimens such as those assembled by the late Dr. Emanuel Libman at the Mount Sinai Hospital in New York City. This fact is worthy of note at the present time, when professors of pathology and anatomy tend to disparage such collections and even to discard them.

From their reading and their preliminary observations Carrel and Tuffier reached two conclusions of overriding importance: (1) that in disease of the heart valves the therapeutic problem was in essence mechanical; and (2) that treatment consisted of replacing stenosis by insufficiency, since stenosis leads to death, whereas insufficiency can be overcome or alleviated by compensatory mechanisms.

In one case of aortic stenosis in man Tuffier had already produced improvement by invaginating the unopened aorta with his finger and tearing the aortic ring.

In their experimental work Carrel and Tuffier followed directly the experiments of Harvey Cushing, adding thereto new methods of incising the valve and an ingenious technique of placing a patch over the operative area.

Another interesting aspect of the work is their novel evaluation of the heart as an object of surgical attack. In paragraphs omitted from the foregoing excerpts they list the surgical danger zones, such as the region of the bundle of His and the cardiac ganglia; and the safe zones, such as the ventricular walls. Their statements resemble those of a military commander who is planning to assault a besieged city.

Since February 1974 the historical articles that have appeared in this series have dealt, as nearly as possible in chronologic order, with experiments on the valves of the heart; three other papers on this subject appeared in 1967.[6–8] This subseries of 11 papers makes it possible to discern a series of stages. In the earliest contributions that have been discussed—those by Cohnheim, Klebs, Rosenbach, Stricker, and others—valvulotomy was performed or attempted mainly in an effort to clarify cardiac physiology. Work of this kind was characteristic of the closing decades of the 19th century. Early in the 20th century MacCallum and Thayer showed that valvulotomy in dogs could throw light on physical signs encountered in human beings and could also be used in classroom instruction. Soon afterward the paper of Cushing and Branch[2] and that of Carrel and Tuffier revealed maturing plans for the surgical treatment of valvular disease in man. Progress was being made, but three decades of additional development were needed before practical benefits were to be gained on any considerable scale.

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Echocardiographic Diagnosis of a Mobile, Pedunculated Tumor in the Left Ventricular Cavity

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A mobile left ventricular tumor was detected by echocardiography The tracing showed a cluster of echoes in the left ventricular cavity corresponding to the location of the tumor as seen in angiograms. A surgery the tumor was attached to the interventricular septum by a thin fibrous stalk.

Primary, pedunculated tumors of the left ventricle are rare. The cas presented here is the first reported instance where such a left ventric ular tumor was diagnosed by echocardiography. We report the cas with special emphasis on its echocardiographic aspects.

Case Report

A 45 year old white, female opera singer was admitted to University of Cal ifornia, Los Angeles Hospital on July 7, 1974 because of left hemiparesis. I the 6 weeks preceding her admission she had symptoms of lightheadnes headaches, blurred vision and scotomas. Two weeks before admission studie by her private physician, which included blood tests, electroencephalogram electrocardiogram, chest X-ray film and upper gastrointestinal series, wer normal except for an erythrocyte sedimentation rate of 34 mm in 1 hour. O admission she had the sudden onset of left arm weakness and facial asymme try. At the time of admission she was noted to have a left facial and lef upper limb paresis with a left upgoing toe. On the 2nd hospital day thes findings partially regressed; a right carotid angiogram showed complete oc clusion of the right internal carotid artery. On the 4th hospital day she com plained of coldness of the right foot and was found to have lost the righ pedal pulses. Three hours later loss of the left pedal pulses ensued. Hepari therapy was started. On the morning of the 5th hospital day she lost the lef femoral pulse and complained of leg pain and coldness.

Past history was negative except for alcohol and amphetamine use severa years previously.

On physical examination the blood pressure was 160/90 mm Hg, puls regular at 72/min and temperature normal. Retinal examination was norma Both common carotid arterial pulses had normal upstroke and volume. Ther was no venous distension. The chest was clear to percussion and auscultation The point of maximal cardiac impulse was normally located; the first an second heart sounds were normal. There was a faint, low frequency, early t mid systolic sound at the apex, which was intermittent and varied with pos ture, while the patient was lying on her left side (Fig. 1). No murmurs or gal lops were present. The left femoral pulse was absent, the right was presen but diminished. There were no popliteal or distal pulses. No bruits wer heard. Both legs were cold and pale. The sedimentation rate was 36 mm in hour, hematocrit 41 percent and white blood cell count 9,000/mm^3. Late fixation titer was 1:140. The electrocardiogram and chest X-ray film wer within normal limits.

An echocardiogram obtained on the 5th hospital day to locate an intracar diac source of emboli showed a cluster of echoes during systole in the outflo tract of the left ventricle between the mitral valve and the interventricula septum (Fig. 1). The abnormal echoes were also seen during diastole as th ultrasonic beam was directed toward the apex (Fig. 2).

A forward left ventriculogram obtained from a pulmonary arterial injec tion showed a highly mobile left ventricular filling defect (Fig. 3) which wa

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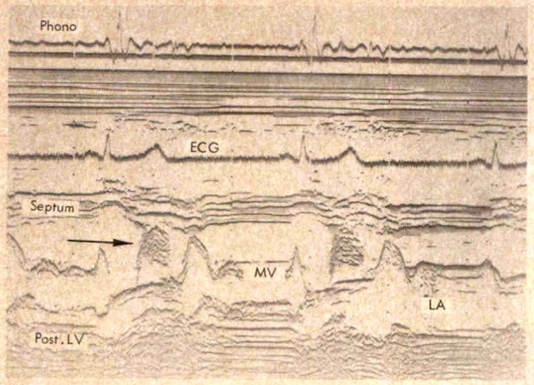

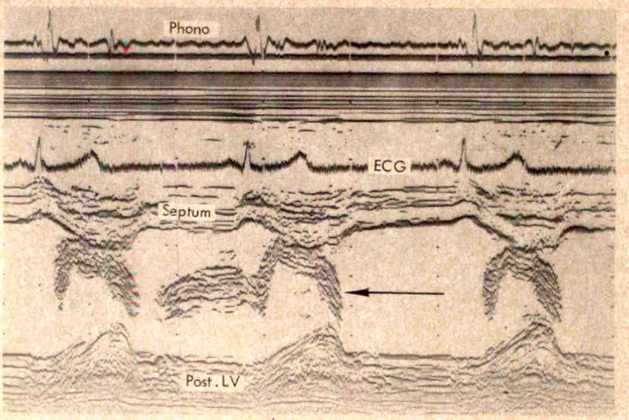

FIGURE 1 (left). Echocardiogram of a left ventricular tumor. The **arrow** points to the tumor-induced cluster of echoes between the interventricular septum and the mitral valve in systole. The simultaneous phonocardiographic (phono) tracing shows an early to mid systolic sound at the time the tumor hits the interventricular septum. ECG = electrocardiograms; LA = left atrium; MV = mitral valve; Post. LV = posterior left ventricular wall.

FIGURE 2 (right). Same recording as in Figure 1 obtained while the ultrasonic beam was directed to the left ventricle below the mitral valve. The **arrow** points to the abnormal echoes that now appear during both systole and diastole.

positioned in the apex during diastole but moved toward the aortic valve in systole. Arteriography demonstrated occlusion of the left common femoral artery and distal right femoral artery.

The patient underwent open heart surgery on the 5th hospital day. When the left ventricle was entered through a ventriculotomy, a 3 cm long tumor was found attached to the lower interventricular septum by a narrow fibrous 1 cm long stalk (Fig. 4). A bilateral femoral embolectomy was also performed. The patient had an uneventful recovery and was discharged home on the 17th hospital day.

Microscopic study of the tumor revealed the findings of a thrombus with early organization. Although a careful search was made by serial sections of the tumor and its stalk, no evidence was found to justify a histologic diagnosis of myxoma. The final pathologic diagnosis was therefore pedunculated thrombus of the left ventricle although the clinical findings and gross morphologic features of the mass were highly suggestive of myxoma. Material removed from the femoral arteries consisted entirely of thrombus.

Discussion

Echocardiography has been used extensively in the diagnosis of atrial tumors since the original description by Effert and Domanig in 1959.[1–5] Our report shows the value of this technique in the diagnosis of

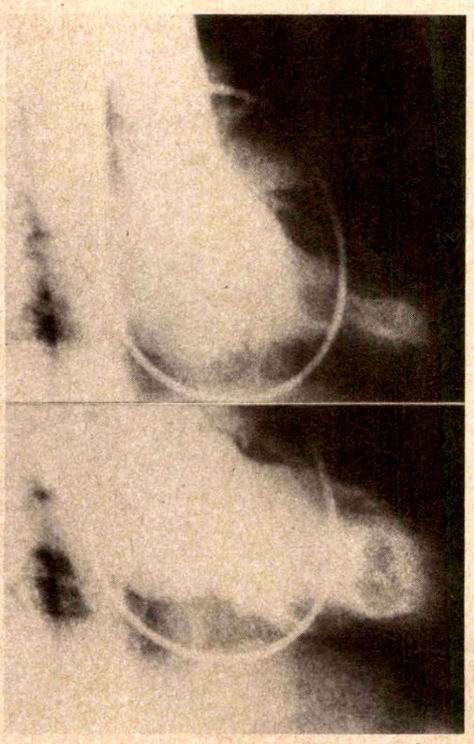

FIGURE 3 (left). Forward left ventriculogram in systole **(top)** and diastole **(bottom).** Note the filling defect caused by the tumor and its mobility with left ventricular contraction.

FIGURE 4 (above). Gross anatomy of the tumor. The tumor is sectioned longitudinally. Note the small stalk that was attached to the lower interventricular septum.

left ventricular tumors. There have been 12 previous case reports of left ventricular myxoma.[6–17] Ventricular tumors may be manifested clinically by a syndrome of outflow tract obstruction simulating valvular disease or by peripheral embolization with or without nonspecific symptoms of low grade fever, malaise and abnormal laboratory findings. There has not been complete agreement on the true nature of these tumors. Their typical occurrence in an otherwise normal heart without any organic or hemodynamic factor of thrombogenesis favors the theory that they are true neoplasms.[18,19]

Our patient manifested multiple emboli. The sedimentation rate was elevated and the latex fixation titer abnormal. The auscultatory findings were intermittent and too subtle to raise the suspicion of intraventricular tumor before the second episode of embolization. Echocardiography is thus a highly recommended tool for detecting a left ventricular tumor in patients who may have few otherwise detectable cardiac abnormalities. It should be useful particularly in the young patient with an unexplained thromboembolic vascular accident.

Acknowledgment

We thank Dr. Mitchel Covel for referring this case to us, and Drs. William G. Hocking and Kenneth B. Wells for helping to care for the patient.

Addendum

Since submission of this manuscript for publication the patient was readmitted to the University of California, Los Angeles Hospital because of unconsciousness. A repeat carotid angiogram showed no change from the previous study. The electrocardiogram on the 2nd hospital day disclosed changes compatible with an acute anteroseptal infarction not present on admission. The echocardiogram failed to show recurrence of an intraventricular mass. A repeat angiocardiogram was considered inappropriate in view of the patient's mental status. The patient has remained comatose for more than 3 months.

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Constrictive Pericarditis in Procainamide-Induced Lupus Erythematosus Syndrome

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A rare case of constrictive pericarditis in procainamide-induced lupus erythematosus syndrome is reported. After 6 months of procainamide therapy fever, pleuritic chest pain, arthralgia and muscle soreness developed in a 47 year old man. These symptoms were soon followed by the onset of acute pericarditis and rapidly accumulating massive pericardial effusion. After withdrawal of procainamide therapy and administration of corticosteroids in large doses, there was marked subjective improvement and rapid reduction in pericardial effusion. However, constrictive pericarditis with massive leg edema and ascites developed 6 weeks after admission as corticosteroid therapy was gradually discontinued. These manifestations subsided after pericardiectomy was performed.

A lupus erythematosus-like syndrome induced by procainamide was first described by Ladd[1] in 1962. Acute pericarditis has been reported in 18 to 57 percent of patients with procainamide-induced lupus erythematosus,[2–4] a rate almost identical to that observed in idiopathic lupus erythematosus (17 to 48 percent).[2,5–7] Large pericardial effusion and cardiac tamponade are uncommon in both forms of lupus.[5,6,8] Constrictive pericarditis is a rare occurrence in idiopathic lupus erythematosus[6,9,10] and, to our knowledge, has not been described in procainamide-induced lupus. We describe a patient with procainamide-induced lupus erythematosus who presented with acute pericarditis and pericardial effusion followed rapidly by constrictive pericarditis as corticosteroid therapy was gradually discontinued.

Case Report

A 47 year old Puerto Rican man was admitted to the New York Veterans Administration Hospital on June 5, 1973 because of low grade fever and pleuritic pain in the left anterior chest of 4 days' duration. Past history revealed chronic alcoholism and cirrhosis of the liver. Four years before admission a portacaval shunt was performed for bleeding esophageal varices. He was found to have multiple ventricular premature systoles 6 months before admission, and since then had been taking 250 mg of procainamide hydrochloride three times daily.

Physical examination revealed a temperature of 100.6° F, pulse rate of 100 beats/min and blood pressure of 100/60 mm Hg. The heart was normal in size. The heart sounds were normal. A grade 2/6 holosystolic murmur was heard at the apex and radiated to the left axilla. The lungs were clear to percussion and auscultation. There was no pleural friction rub. The liver and the spleen were enlarged. Palmar erythema and spider angiomas were present. The hemoglobin was 13.1 g/100 ml, (white blood cell count 5,400/mm^3 and the erythrocyte sedimentation rate was 61 mm in 1 hour. The electrocardiogram revealed sinus tachycardia and a few ventricular premature systoles.

One week after admission he had pain in the small joints of both hands, tenosynovitis of the extensor tendons of both big toes, generalized muscle soreness and dyspnea. The temperature was 103° F, the pulse rate 120 beats/min and the blood pressure 110/90 mm Hg. Pleural and pericardial friction

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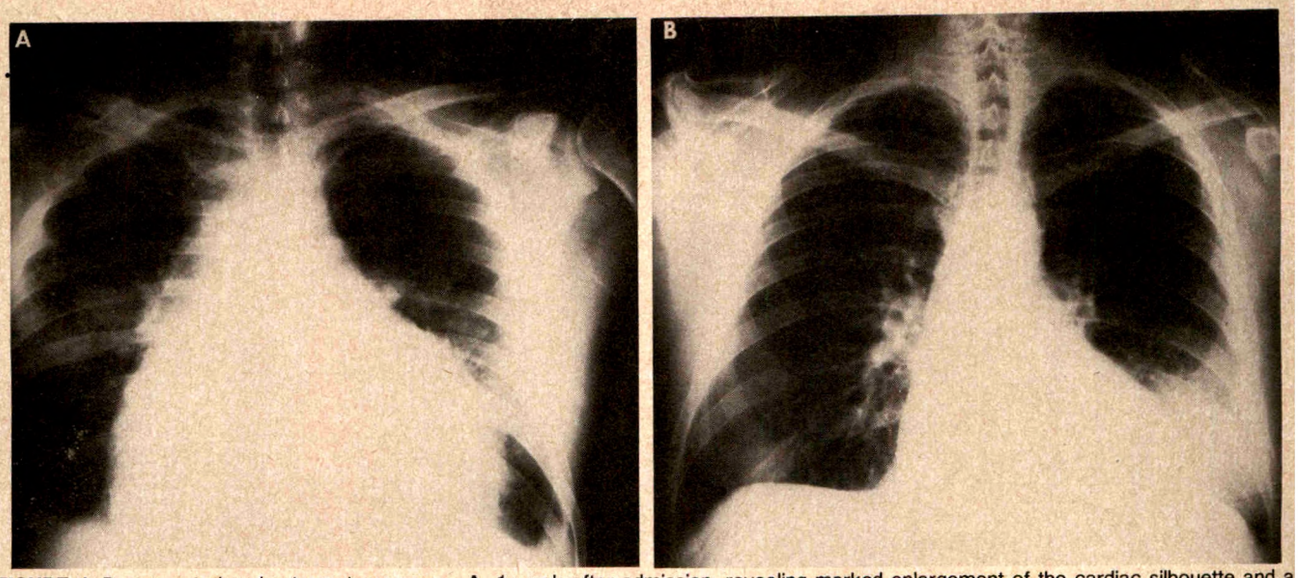

FIGURE 1. Posteroanterior chest roentgenograms. **A,** 1 week after admission, revealing marked enlargement of the cardiac silhouette and a small left pleural effusion. **B,** at the time of right heart catheterization.

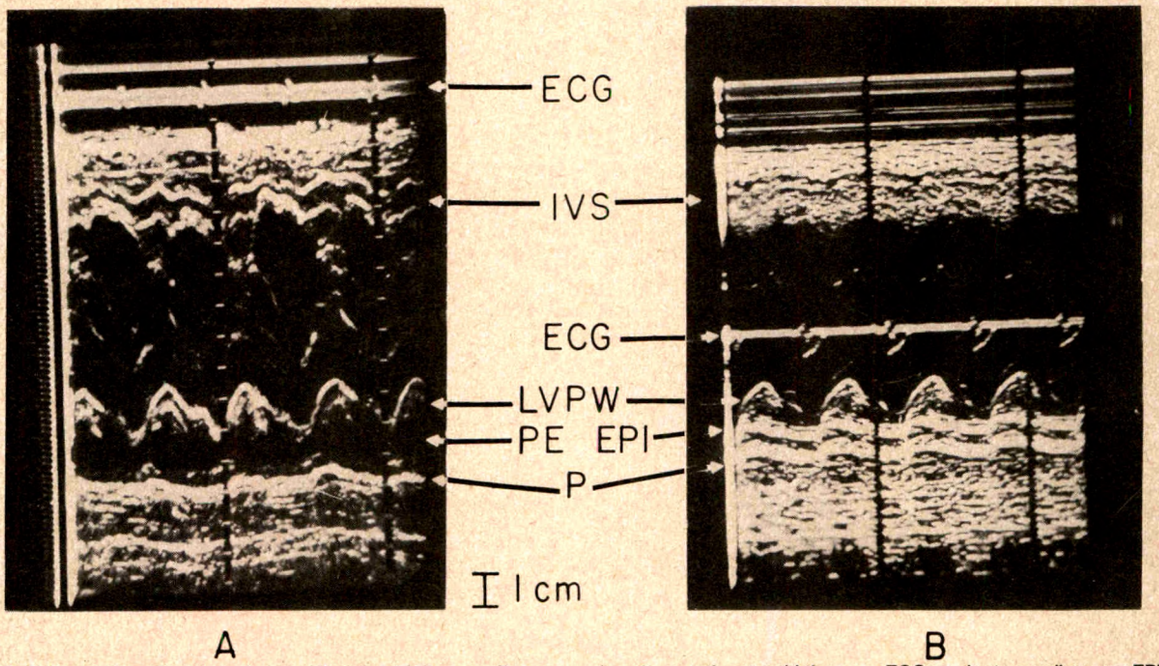

FIGURE 2. Echocardiograms. **A,** before corticosteroid therapy. **B,** two weeks after corticosteroid therapy. ECG = electrocardiogram; EPI = epicardium; IVS = interventricular septum; LVPW = left ventricular posterior wall; P = pericardium; PE = pericardial effusion.

rubs were heard. Two days later he became severely dyspneic. The heart sounds were distant. The chest roentgenogram revealed a markedly enlarged cardiac silhouette and a small left pleural effusion (Fig. 1A). The electrocardiogram disclosed a nondiagnostic repolarization abnormality. The central venous pressure was 20 cm water. The echocardiogram showed evidence of a large pericardial effusion (Fig. 2A).

The lupus erythematosus cell preparation was negative. The immunofluorescent test for antinuclear antibodies was positive at a titer of 1:512. The latex fixation test for rheumatoid factor was positive at a titer of 1:320. The serologic test for anti-deoxyribonucleic acid antibodies was negative as were the skin tests for tuberculosis and fungal diseases and blood and urine cultures. The diagnosis of procainamide-induced lupus erythematosus with pericarditis and pericardial effusion was made.

Clinical Course

The patient was treated with 60 mg of prednisone daily. There was marked subjective and objective improvement in his clinical condition. Two weeks later the chest X-ray film disclosed marked reduction in the size of the cardiac silhouette. The echocardiogram revealed a minimal echo-free space between the pericardium and the posterior left ventricular wall (Fig. 2B). The echoes reflected from the pericardium and the epicardium were dense, suggesting thickened epicardium and pericardium.

Over the next 2 weeks the dose of prednisone was gradually tapered. However, 1 week later dyspnea, orthopnea, ascites and dependent edema developed. The neck veins were markedly engorged, and the blood pressure was 110/90 mm Hg with an inspiratory decrease in systolic pressure of 12 mm Hg. The chest X-ray film revealed a slightly enlarged cardiac silhouette (Fig. 1B). The immunofluorescent test for antinuclear antibodies was positive at a titer of 1:256 and the latex fixation test for rheumatoid factor was positive at a titer of 1:60.

Right heart catheterization was performed (Table I). The right atrial and right ventricular pressure curves were suggestive of restriction to diastolic filling. The cardiac output was high, probably due to peripheral arteriovenous shunts. An intracardiac left to right shunt was excluded by the hydrogen appearance time of 8 seconds in the main pulmonary artery. The right atrial angiogram revealed a distance of 1 cm between the right atrial endocardium and the right border of the cardiac silhouette. These findings were suggestive of either pericardial effusion or pericardial constriction with thickened pericardium.

Surgery was performed for pericardial exploration. At operation, very little fluid was present in the pericardial sac. The pericardium was markedly thickened, measuring 5 to 7 mm in some areas. It was adherent to the epicardium and could be separated only with great difficulty. Partial pericardiectomy was performed. Histologic examination of the pericardium showed dense collagenous tissue and extensive highly vascularized granulation tissue. The acid-fast stain and the culture for mycobacteria revealed nothing abnormal.

After surgery the patient's condition improved with disappearance of ascites and leg edema. He was permitted to leave the hospital on a weekend pass and returned in a drunken state. There was rapid progression to hepatic coma, massive gastrointestinal bleeding, Klebsiella sepsis and death.

TABLE I

Hemodynamic Findings

Site	Pressure (mm Hg)
Right atrium	(10)
Right ventricle	31/16
Pulmonary artery	31/16 (20)
Pulmonary wedge	(13)
Brachial artery	163/63 (91)
Cardiac index (liters/min per m^2)	6.9
Arterial-mixed venous O_2 difference (ml/liter)	24
Hydrogen appearance time in pulmonary artery (sec)	8

Figures in parentheses represent mean pressures.

Discussion

The diagnosis of procainamide-induced lupus erythematosus in this patient was made on the basis of the clinical manifestations and the presence of antinuclear antibodies in the serum. Although the lupus erythematosus cell phenomenon is demonstrable in 75 to 86 percent of patients with procainamide-induced lupus, it may be absent, as it was in our patient.[2,3] The incidence of acute pericarditis is almost identical in idiopathic and procainamide-induced forms of lupus erythematosus[2–7] whereas large pericardial effusion and cardiac tamponade are uncommon in both forms.[5,6,8] Constrictive pericarditis is extremely rare in idiopathic lupus erythematosus.[6,9,10]

Pericardial constriction developed in this patient with striking rapidity, occurring 6 weeks after the onset of acute pericarditis. The patient with idiopathic lupus erythematosus described by Starkey and Hahn[10] also had constrictive pericarditis within 7 weeks after the onset of acute pericarditis. In both patients corticosteroid therapy was gradually withdrawn 5 to 6 weeks after it was begun. The relatively rapid withdrawal of corticosteroid therapy in our patient as well as in the patient described by Starkey and Hahn could have precipitated a panmesenchymal and panangiitic reaction of Slocumb.[11] Although this reaction is uncommon, its occurrence in the presence of resolving fibrinous pericarditis may have caused rapid deposition of collagen and fibrous tissue leading to pericardial constriction. If this mechanism is correct, corticosteroid drugs in such patients should be withdrawn over a few months instead of a few weeks.

A majority of patients receiving procainamide have underlying cardiac disease to which the manifestations of pericardial involvement may be attributed unless the possibility of cardiac involvement by procainamide-induced lupus erythematosus is suspected. Consideration of this possibility is particularly important since cessation of procainamide with or without corticosteroid therapy will abate the symptoms in a majority of patients.[2]

Acknowledgment

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Severe Alcoholic Cardiomyopathy Reversed with Abstention from Alcohol

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In a chronic alcoholic with a severe congestive cardiomyopathy the angiographic and hemodynamic evidence of left ventricular dysfunction was completely reversed after 1 year of abstinence. At the time of initial presentation two of the traditional hallmarks of a poor prognosis were present, namely, a long exposure to alcohol before the onset of symptoms and severe diffuse left ventricular dilatation and hypokinesis (ejection fraction 14.9 percent). Yet, today, 18 months later he is asymptomatic, receiving no medications and has normal left ventricular function. A reexamination of prognostic factors in alcoholic cardiomyopathy may be indicated.

We recently performed a complete hemodynamic investigation in an alcoholic patient on two separate occasions 1 year apart. The first study showed evidence of a severe congestive cardiomyopathy. The second study followed a year of almost total abstinence and revealed that all hemodynamic and angiographic variables had returned to normal; the signs and symptoms of congestive failure present at the time of the first study had also resolved. Other than the change in alcoholic consumption, there was no other significant alteration in this patient's life style or activity level in the year between investigations and a period of complete bed rest was not instituted after the first study. This report suggests that even patients with a long history of excessive alcoholic consumption and severe diffuse left ventricular dysfunction may still have a potentially totally reversible situation.

Case Report

The patient is a 49 year old man who was well until August 1972 when he noticed the appearance of easy fatigability, followed by increasing dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ankle edema and palpitations. There was no history of chest discomfort. There were no symptoms suggestive of a viral illness before the onset of the symptoms cited. There was a history of heavy alcoholic intake for at least 20 years with a daily consumption of about 16 oz. of whiskey. Nevertheless his food intake and nutrition were good and he was a productive and successful businessman. He was also a heavy chronic cigarette smoker. There was no history of hypertension.

He was given standard treatment for congestive heart failure but was admitted to a local hospital on three occasions between September and December 1972 because of recurrent refractory congestive failure.

He was admitted to the Toronto General Hospital on December 14, 1972 for further investigation. He appeared well nourished and there were no stigmata of chronic liver disease. The peripheral arterial pulses were irregular and thready. His limbs were cool. Blood pressure was 90/70 mm Hg. The mean jugular venous pressure was 5 cm above the sternal angle with normal respiratory variation. There was no palpable precordial impulse; there were no murmurs and a third heart sound was not heard. The second sound was normally split. The liver was palpable 3 cm below the right costal margin and was smooth and nontender. The spleen was not palpable. There was no ankle edema.

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The initial electrocardiogram (Fig. 1A) showed atrial fibrillation, low voltage in the standard leads and poor R wave voltage across the precordial leads. The chest X-ray film (Fig. 2A) disclosed cardiomegaly. Routine pulmonary function tests, thyroid function indexes, sedimentation rate and serum protein determinations were normal. A lupus erythematosus cell test was negative.

Cardiac catheterization was performed on December 20, 1972. Right heart oxygen sampling showed no evidence of a left to right intracardiac shunt. There was no evidence of valvular heart disease. The coronary arteries were normal angiographically. The left ventriculogram was obtained using a Brockenbrough transseptal catheter. The hemodynamic and angiographic data (Table I) revealed evidence of severe left ventricular dysfunction. Representative end-diastolic and end-systolic frames of the left ventriculogram are shown in Figure 3.

On the basis of these data, a diagnosis of a severe congestive cardiomyopathy was made. In the absence of any other obvious cause it was assumed that alcoholism was the primary factor in the development of the myopathy and the patient was urged to stop his alcoholic consumption.

He was discharged on December 28, 1972 on a regimen of digoxin, 0.375 mg/day; furosemide, 40 mg/day, potassium supplements; quinidine, 200 mg four times a day, and sodium warfarin for anticoagulation. For the next 4 months he did not smoke or drink alcohol. In May 1973 he began to drink about 2 to 4 oz. of whiskey a week and his alcoholic consumption has not exceeded this amount up to the present time. He remains a nonsmoker.

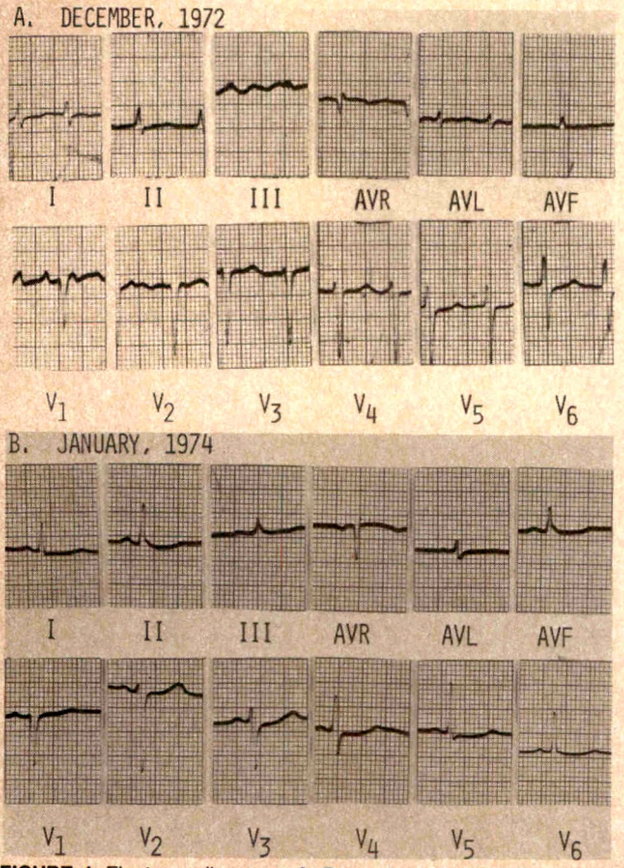

FIGURE 1. Electrocardiograms. **A,** December 14, 1972; **B,** January 6, 1974.

TABLE I

Hemodynamic and Angiographic Data

	Dec. 20, 1972	Jan. 7, 1974
Rhythm	Atrial fibrillation	Sinus
Cardiac index (liters/min per m^2)	2.04	2.73
Pressures (mm Hg)		
PA mean	31.0	13.0
RVEDP	5–9	4–7
LA mean	24.0	5.0
LVEDP	16–25	4–7
LV volumes (ml/m^2)		
End-diastolic	118	88
End-systolic	100	24
LV ejection fraction (%)	14.9	72.5
LV angiogram	Severe diffuse hypokinesis	Normal

LA = left atrial; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; PA = pulmonary arterial; RVEDP = right ventricular end-diastolic pressure.

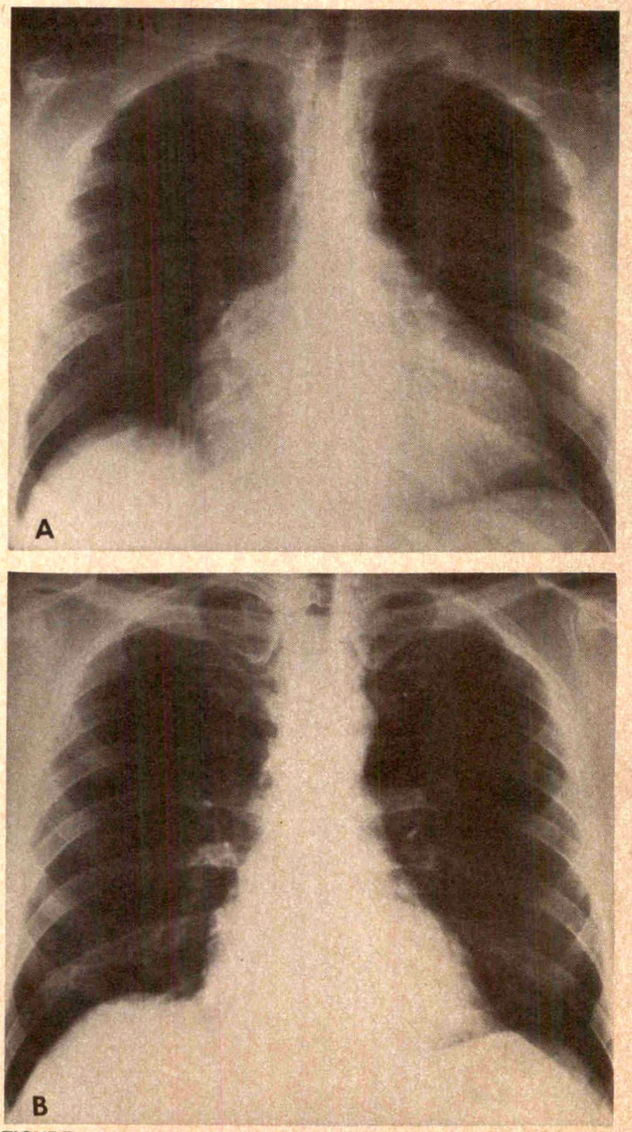

FIGURE 2. Posteroanterior chest X-ray films. **A,** December 14, 1972, shows cardiomegaly with a cardiothoracic ratio of 20.5/33.0. **B,** January 6, 1974. Heart size is now within normal limits; the cardiothoracic ratio is 16.0/33.0.

In February 1973, his rhythm reverted from atrial fibrillation to a normal sinus mechanism. By April 1973 he was asymptomatic, his exercise tolerance was normal and there were no signs of heart failure. He had returned to full time employment. The furosemide and potassium were discontinued without any adverse effects.

He was admitted again in January 1974 for a repeat cardiac catheterization.The electrocardiogram on this admission (Fig. 1B) revealed sinus rhythm and was normal except for digitalis-induced S-T sagging. By comparison with the tracing of December 1972, the voltage in the standard leads had increased and the R waves were higher across the precordial leads. Comparison of the chest X-ray film (Fig. 2B) with the one obtained in December 1972 showed a significant reduction in heart size. The results of the catheterization on this admission are summarized in Table I. Representative end-diastolic and end-systolic frames of the left ventricular angiogram are shown in Figure 4. It is clear that complete resolution of the hemodynamic and angiographic evidence of severe left ventricular dysfunction had occurred in the intervening year.

On the basis of these findings all medications were discontinued and the patient has remained well and asymptomatic up to the present time.

Discussion

The criteria for the diagnosis of alcoholic cardiomyopathy proposed by McDonald et al.[1] include (1) the appearance of signs and symptoms of cardiomyopathy with persistent cardiomegaly, (2) inability to establish an etiologic basis for the heart disease other than heavy alcohol consumption, and (3) a history of prolonged consumption of excessive amounts of alcohol. Our patient satisfied these criteria and the diagnosis is further strengthened by the reversal of the disease process with cessation of alcohol consumption. The possibility that this man had a viral myocarditis cannot be absolutely excluded. However there were no symptoms of a viral illness preceding the appearance of congestive heart failure and spontaneous resolution of a severe congestive cardiomyopathy of viral origin would be unlikely.

To our knowledge this is the first report of a case of alcoholic cardiomyopathy in which complete reversibility after abstention from alcohol has been documented by cardiac catheterization and angio

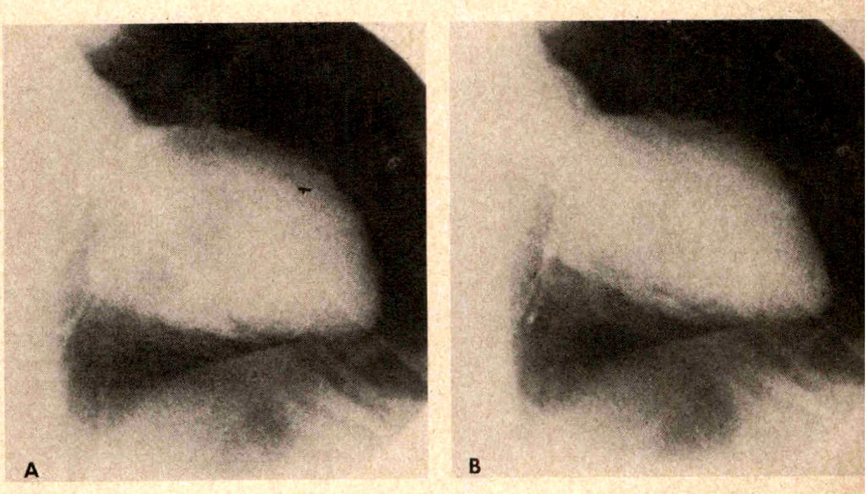

FIGURE 3. December 20, 1972. Single end-diastolic **(A)** and end-systolic **(B)** frames from a 35 mm cineangiogram of the left ventricle in the right anterior oblique view. The ejection fraction was 14.9 percent.

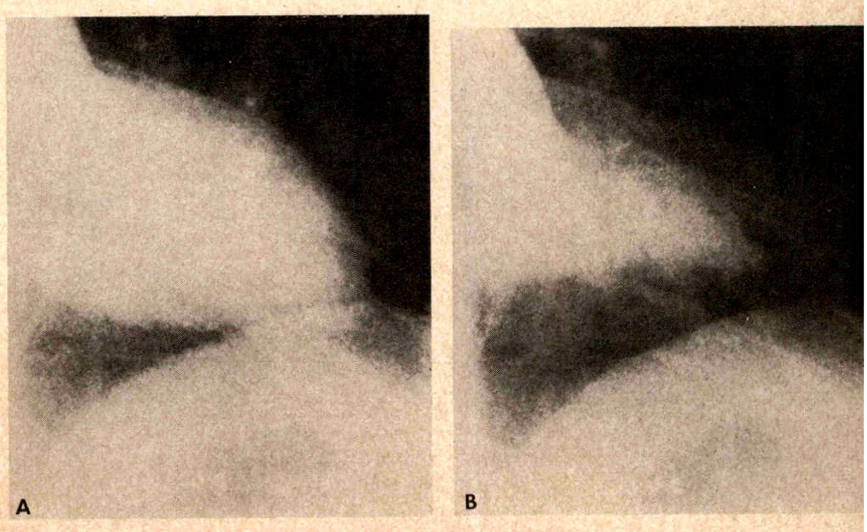

FIGURE 4. January 7, 1974. Single end-diastolic **(A)** and end-systolic **(B)** frames from a 35 mm cineangiogram of the left ventricle in the right anterior oblique view. The ejection fraction was 72.5 percent.

graphic studies. In a recent publication, Demakis et al.[2] reported on the natural course of 57 patients with alcoholic cardiomyopathy and they found a statistically significant relation between abstention from alcohol and improvement in clinical status. The improvement in their patients, however, was determined by noninvasive means such as chest X-ray films and was not documented angiographically. Also, their data suggest that none of the patients with subsequent improvement had the degree of congestive heart failure or cardiomegaly manifested by our patient at the time of presentation.

Myocardial biopsy was not performed in our case. However, one might speculate on the pathologic features present at the time of the initial investigation and associated with subsequent resolution. It is likely that little or no fibrosis was present. Generalized swelling of the endoplasmic reticulum without disorganization has been shown to be an early and unique manifestation of myocardial damage in alcoholic cardiomyopathy.[3] Mitochondrial swelling has also consistently been described in this form of cardiomyopathy. It is possible that these ultrastructural abnormalities existed in a severe and diffuse form in our patient at the time of presentation and accounted for the severe left ventricular dysfunction documented at the first study. These abnormalities could have resolved with subsequent abstention from alcohol. The foregoing is a possible explanation for the return to normal left ventricular function in our patient.

Clinical implications: This report is clinically important from at least two standpoints. First, a controversy exists as to the mechanism of improvement in patients with alcoholic cardiomyopathy who follow a favorable course. McDonald et al.[1] have attributed this improvement, at least in part, to a trial of prolonged bed rest. On the other hand, other studies[2–4] have shown a similar success rate with abstention from alcohol alone and no restriction of activities. Our case favors the latter experience since a period of bed rest was not instituted. Second, at the time of presentation our patient had the clinical and hemodynamic features usually indicative of an irreversible situation and a poor prognosis, namely, a long history of alcoholism[4] and diffuse left ventricular dilatation and dysfunction.[5] Yet, with abstention from alcohol, his cardiac function returned to normal and he became asymptomatic. This report suggests a more encouraging prognosis for alcoholics with cardiomyopathy than is generally realized. Possibly, if this information were conveyed to such patients, there might be a greater number who would be motivated to abstain totally and permanently. Further serial hemodynamic studies on such patients would be helpful in substantiating the findings in the patient herein reported.

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Holt-Oram Syndrome Associated with Combined Ostium Primum and Secundum Atrial Septal Defects: Successful Surgical Closure

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A 55 year old man with the typical findings of Holt-Oram syndrome except for the presence of a septum primum defect in addition to the usual secundum defect is described. The clinical, physical, radiologic and operative findings are presented.

Oppenheimer et al.[1] first described in 1949 a clinical entity consisting of anomalies of the osseous system in conjunction with atrial septa defect. In 1960, Holt and Oram[2] described in greater detail this syn drome of familial heart disease associated with skeletal malforma tions that now bears their name. Forty-seven cases of the Holt-Oran syndrome have been reported; in 17 an atrial septal defect of the se cundum type was surgically corrected.[3] This report is the first to de scribe a patient with the Holt-Oram syndrome in whom an ostiun primum defect in addition to a secundum defect was noted and surgi cally corrected.

Case Report

A 55 year old man was admitted to our outpatient department in Augus 1973 with a 3 year history of exertional dyspnea, tachycardia and recurren congestive heart failure. He had been treated with digitalis and diureti agents for 2 years. He was a chronic alcoholic.

Physical examination showed no cyanosis or clubbing of the digits. Th jugular veins were slightly dilated. The lungs were clear. The blood pressur was 150/90 mm Hg; heart rate was 110/min with a slightly irregular rhythm A grade 2/4 systolic murmur was audible at the third intercostal space to th left of the sternal border. There was a diastolic rumble at the apex with fixe splitting of the second sound in the pulmonary area. Examination of the os seous system revealed congenital anomalies of both thumbs evidenced by hy poplasia of the thenar eminences. There was radiographic evidence of bilater al hypoplasia of the greater multangular bones that caused the base of th first metacarpal bone to be directed medially and to articulate in the sam plane as the other metacarpals. Both thumbs simulated the configuration o fingers and had only two phalanges. The clavicles were abnormally shor causing the shoulders to project forward.

Radiologically, the heart was over 25 percent larger than the predicted siz for the patient's height and weight. The lungs showed advanced bilateral pul monary congestion with increased vascular markings and evidence of emphy sema. All laboratory findings were within normal limits. The electrocardio gram and vectorcardiogram revealed atrial fibrillation, right ventricular hy pertrophy and left axis deviation.

Cardiac catheterization studies revealed a step-up of oxygen saturatio from 67 percent in the superior vena cava to 77 percent in the right atriun and 88 percent in the right ventricle. The mean right atrial pressure wa 55/25 mm Hg. The left to right shunt was five times greater than the cardia output. The pulmonary vascular resistance was 0.7 unit (normal). Cineangi ography demonstrated an enlarged left atrium with shunting of dye at bot the atrial and ventricular levels. There was no mitral or tricuspid regurgita tion. Both coronary arteries were patent and smooth.

The clinical, physical and radiologic findings were all consistent with th classic description of the Holt-Oram syndrome except for the presence of a

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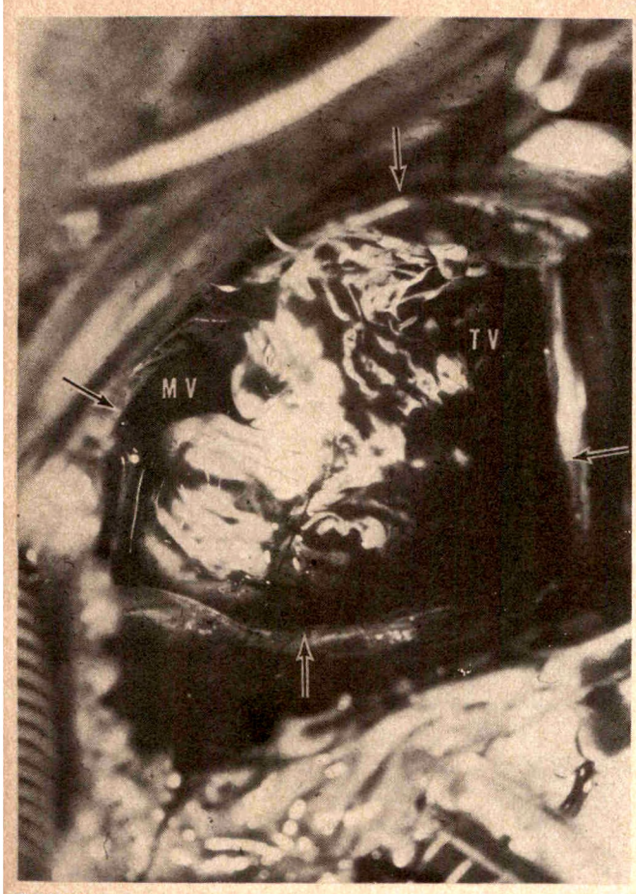

FIGURE 1. Photograph taken at operation through the right atriotomy showing the 4 by 4 cm ostium primum type atrial septal defect. The mitral (MV) and tricuspid (TV) valves are visible through the defect (**arrows**).

atrial septal defect of the ostium primum rather than secundum type. Surgical correction was recommended.

Operative Findings

On September 20, 1973 a right atriotomy was performed with use of total cardiopulmonary bypass (Kay-Cross oxygenator) and hypothermic arrest. A 4 by 4 cm endocardial cushion defect was present without mitral or tricuspid valve dysfunction (Fig. 1). There was also a smaller secundum defect approximately 1 cm in diameter located just below the superior vena caval inlet. The septum primum defect was closed with a pericardial patch. Care was exercised to avoid the conduction system at the atrioventricular (A-V) aspect of the defect. The secundum defect was closed by direct suture.

Upon rewarming and restarting the heart a normal sinus rhythm was present that continued until the 6th postoperative day when bradycardia developed, and pacing was required. On the 8th postoperative day complete A-V block developed that persisted for 4 days. The patient was given digitalis and his condition steadily improved. He was discharged 3 weeks postoperatively with regular sinus rhythm.

Discussion

The criteria for recognition of a Holt-Oram syndrome consist of a familial history of an atrial septal defect of the secundum type in conjunction with typical deformities of the limbs. The patient stated that his mother (now deceased) had similar thumb abnormalities. Various terms,[4–6] such as atrio-digital dysplasia or upper limb cardiovascular syndrome, have been used to describe the osseous abnormalities found in the Holt-Oram syndrome.

The majority of patients have an arrhythmia.[4–6] A wandering pacemaker was the most commonly described rhythm disturbance and was attributed to congenital myocardial disease. Incomplete right bundle branch block patterns were observed when there was an atrial septal defect. This, as well as atrial fibrillation, was observed in our case. However, immediately postoperatively, when the patient was still on the operating table, the cardiac monitor revealed a normal sinus rhythm without atrial fibrillation. The patient continued to have regular sinus rhythm for the first 6 postoperative days when bradycardia developed followed by complete A-V block within two days; this required temporary cardiac pacing. We assume that the bradycardia and block were the result of an edematous reaction along the conduction system adjacent to the pericardial patch closure of the large ostium primum defect.

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Unilateral Pulmonary Vein Atresia: Diagnosis and Treatment

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The clinical, hemodynamic, angiographic and pathologic features o unilateral pulmonary vein atresia in a 16 month old boy are described The relevant findings were symptoms and signs of influenza, roentgen ographic evidence of unilateral diffuse interstitial edema, prominent in terlobar fissures and pleural effusion, absence of abnormal cardia structure and prominent unilateral bronchial circulation. Angiocardi ography was necessary for a definitive diagnosis and revealed the lacl of a site of entry for venous blood from the right lung into the circula tion. The patient was treated successfully by a right pneumonectomy The histologic hallmark in this case was extensive intimal fibrosis o the pulmonary veins.

Congenital unilateral pulmonary vein atresia produces a unique he modynamic profile that results in clinical findings entirely differer from those of bilateral pulmonary venous obstruction. In this pape we describe an anomaly that caused unilateral obstruction to pulmc nary venous return. The anomaly was difficult to recognize clinicall and required cardiac catheterization and angiography for definitiv diagnosis. The favorable prognosis after surgical treatment prompte us to report this case.

Case Report

A 16 month old Caucasian boy was referred to the Texas Children's Hosp tal with a diagnosis of right pleural effusion. He had been born premature (weight 1.58 kg) after an otherwise uncomplicated prenatal course and deliv ery. The neonatal course was uneventful, and the infant was discharged fro the nursery at age 1 month weighing 2.25 kg. He had two upper respirator infections during the 1st year of life, and his growth and development we normal.

At age 1 year, he had a febrile illness with cough for 1 week, and a che roentgenogram was interpreted as indicating pneumonia in the right lun Films taken 1 week later were reported to reveal an unresolved infiltrate i the lower lobe of the right lung. Two months later, fever and cough recurre and again there was radiographic evidence of right-sided pneumonia. Th fever subsided but the cough persisted and the right lung remained rad opaque. Physical examination at that time revealed dullness to percussic and respiratory rales over the right lung.

Evaluation for recurrent pneumonia included hemograms, analysis sweat electrolytes, determination of fungal and cold agglutinins and myc plasma titer, electrophoresis of serum proteins, skin tests for fungi and tube culosis and gram and acid-fast stains of tracheal aspirate; the results were a normal or negative. Culture of the tracheal aspirate grew Haemophilus i fluenzae. Slight clinical improvement was noted only after pulmonary su portive treatment with postural drainage and a nebulizer mask with Mucon yst®. Because the radiographic abnormality persisted, the patient was admi ted to Texas Children's Hospital for additional diagnostic studies.

Physical examination revealed a well developed playful boy in no distres Respiratory rate was 30/min and heart rate 140 beats/min with normal p ripheral pulses. There was no cyanosis of the lips or nail beds or clubbing

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the digits. There was dullness to percussion, and breath sounds were decreased over the right posterior chest wall. The heart was not enlarged and there were no murmurs or extra sounds. Other physical findings were noncontributory.

The chest roentgenograms on admission (Fig. 1) revealed on the right side only, a diffuse increase in the interstitial and vascular markings associated with Kerley B lines, an interlobar fissure and a thickened right pleura with effusion. The electrocardiogram was normal. The laboratory tests were repeated with normal or negative results. A right thoracentesis produced 60 cc of serosanguinous exudate with a specific gravity of 1.027 and protein content of 2.16 g/100 ml. Viral, fungal and bacterial organisms failed to grow from a culture of the pleural fluid.

Isotope images obtained by repeated inhalation of xenon-133 revealed markedly decreased ventilation of the right lung. Images obtained by perfusion of the lungs with technetium-99m human albumin microspheres revealed almost no perfusion of the right lung. Ventilation and perfusion of the left lung were normal.

Cardiac catheterization demonstrated that oxygen saturation of the blood was greater in the right than in the main pulmonary artery (Table I). The wedge pressure in the right pulmonary artery was significantly greater than that in the left artery. Hydrogen curves confirmed that left to right shunting occurred distal to the pulmonary valve.

A serial biplane angiocardiogram with injection of contrast medium into the main pulmonary artery demonstrated a small right pulmonary artery that was less opaque than the left artery (Fig. 2A). There was marked preferential flow to the left pulmonary artery, and the pulmonary capillaries could be seen only in the left lung. The levophase (Fig. 2B) demonstrated two left pulmonary veins emptying into a normal left atrium. The right pulmonary veins could not be seen, and the right border of the left atrium appeared smooth showing no reflux of contrast material into the right pulmonary vein during atrial systole. The delayed sequence frames (Fig. 2C) revealed no right pulmonary venous drainage. However, prominent bronchial arteries to the right lung were demonstrated during the levophase.

Selective cineangiograms of the right pulmonary artery demonstrated a flow of contrast material from the right pulmonary artery to the left lung. A prolonged sequence at 12 frames/sec was obtained after a slow injection of contrast material into the lower lobe of the right lung through a catheter in the pulmonary arterial wedge position (Fig. 3); this sequence revealed delayed emptying of the opaque material from the right pulmonary bed. Eventually a fine, tortuous venous network appeared, which we believe represented bronchial veins draining into the azygos vein.

Surgical treatment: With this information, a diagnosis of pulmonary venous obstruction secondary to atresia of the right pulmonary veins was made. Pneumonectomy was recommended, although we proposed that surgical anastomosis of the right pulmonary veins be attempted instead if adequate right pulmonary veins were found near the left atrium during surgical dissection.

At operation, multiple adhesions in the right pleural cavity and a thick pleura could be seen. The right lung was edematous, boggy and congested, resembling a sequestered lung. An enlarged azygos vein and large, tortuous bronchial arteries were found. The right pulmonary veins were atretic and were connected to the left atrium by only a strand of tissue. A right pneumonectomy was performed. The patient had an uneventful recovery and, at discharge, had normal arterial blood gas values with a femoral arterial oxygen saturation level of 98 percent.

Pathology

Gross findings: The pleural surface of the right lung was thickened with fibrous adhesions that bound the three lobes together. Fresh focal hemorrhages were present. The right pulmonary artery and its branches were identified at the hilus. There were several smaller ligated vessels, 1 to 2 mm in diameter, along the hilar surface, most extending toward the apex of the lung and entering from the pleura at points removed from the main bronchus. Fewer small thickened vessels were found toward the base of the lower lobe. Injection of contrast material (Hypaque®) into the main right pulmonary artery after resection delineated the major branches of the artery in all lobes of the lung. A second injection of more dense contrast material (barium) into one of the small vessels entering the upper lobe delineated more tortuous, smaller vessels within the lobe. These corresponded to the bronchial arteries observed in the preoperative angiograms. Neither a single vein nor a complex of ve-

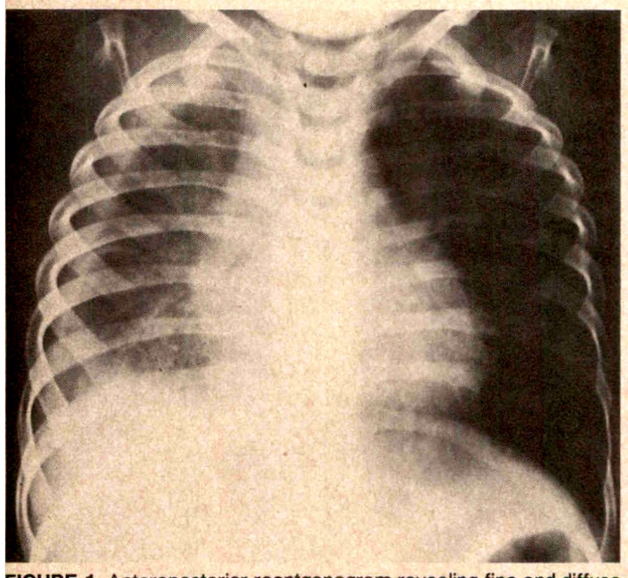

FIGURE 1. Anteroposterior roentgenogram revealing fine and diffuse increase in the interstitial and vascular markings, Kerley B lines, an interlobar fissure and pleural effusion, all only in the right lung field.

TABLE I

Cardiac Catheterization Data

Site	Oxygen Saturation (%)	Pressures (mm Hg)
Superior vena cava	76	. . .
Right atrium	75	(6)
Right ventricle	75	28/6
Main pulmonary artery	75	28/14(20)
Proximal right pulmonary artery	83	24/18(21)
Distal right pulmonary artery	89	24/18(21)
Right pulmonary arterial wedge	. . .	(20)
Left pulmonary artery	76	22/14(19)
Left pulmonary arterial wedge	. . .	(12)
Femoral artery	95	84/60(72)

Figures in parentheses indicate mean pressure.

nous channels was identified in the lower segment of the lung that might have corresponded to the channel draining into the azygos vein as seen in the angiograms.

On cut section, the lung was focally fibrotic with irregular yellow streaks in the parenchyma. However, most of the lung appeared well aerated.

Microscopic findings: Atelectasis, congestion and edema were the most notable microscopic changes in the pulmonary parenchyma. Lymphatic vessels in the pleura and the interlobular septa just beneath the pleura were strikingly dilated. Focal fibrosis in the parenchyma was noted.

Many of the small pulmonary arteries showed medial hypertrophy and some vessels had endothelial proliferation (Fig. 4, left). There were no thrombi in the pulmonary arteries. Bronchial arteries in sections from the upper pulmonary lobe contained barium. An occasional pulmonary artery of medium size also contained barium, thus indicating communication between the bronchial and pulmonary arteries.

Small venous channels in the peripheral parenchyma of the lung showed extensive intimal fibrosis with severely compromised lumens (Fig. 4, right). Larger pulmonary veins showed similar sclerosis; however, atresia was not detected in the sections randomly selected for microscopic examination.

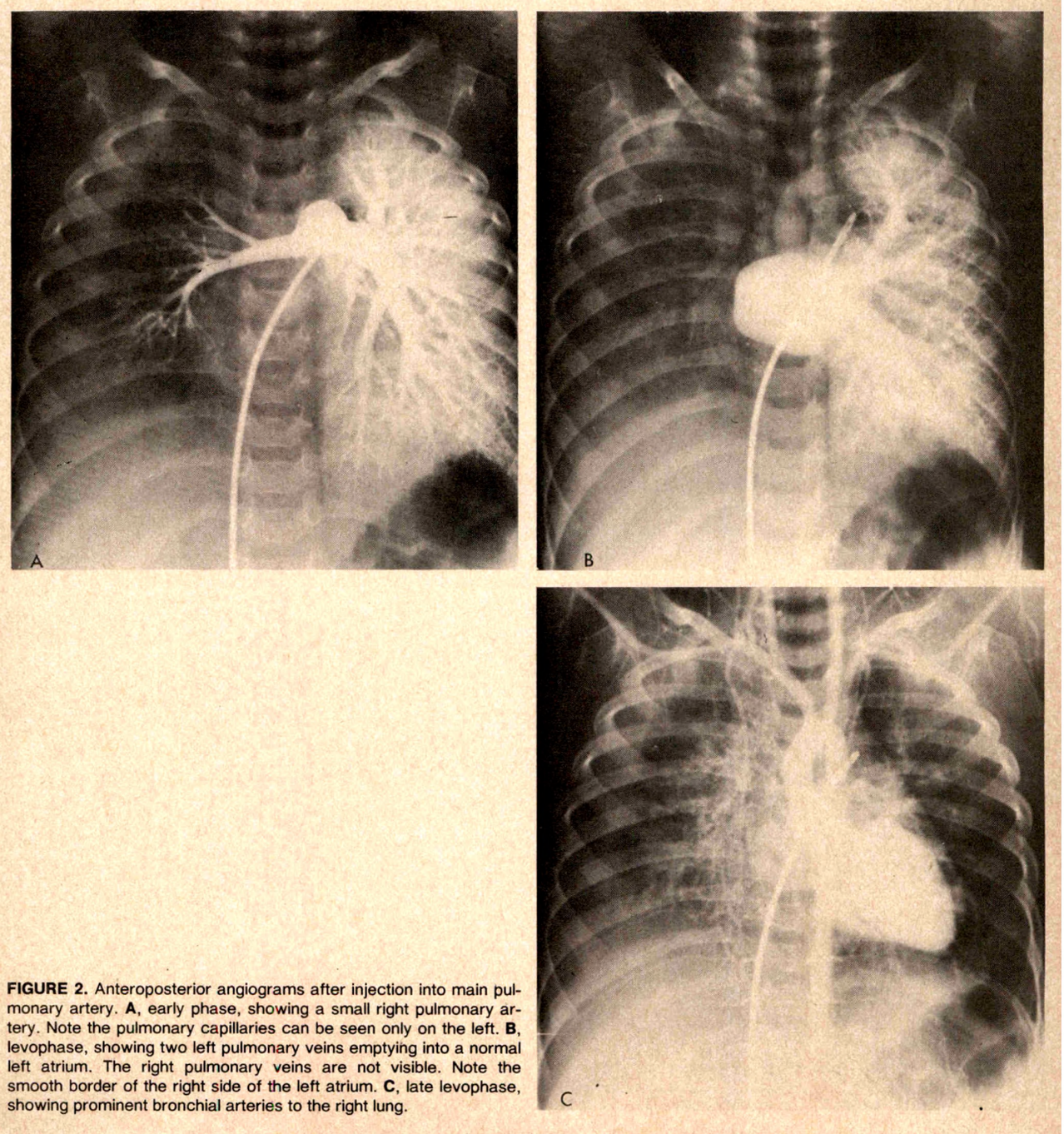

FIGURE 2. Anteroposterior angiograms after injection into main pulmonary artery. **A**, early phase, showing a small right pulmonary artery. Note the pulmonary capillaries can be seen only on the left. **B**, levophase, showing two left pulmonary veins emptying into a normal left atrium. The right pulmonary veins are not visible. Note the smooth border of the right side of the left atrium. **C**, late levophase, showing prominent bronchial arteries to the right lung.

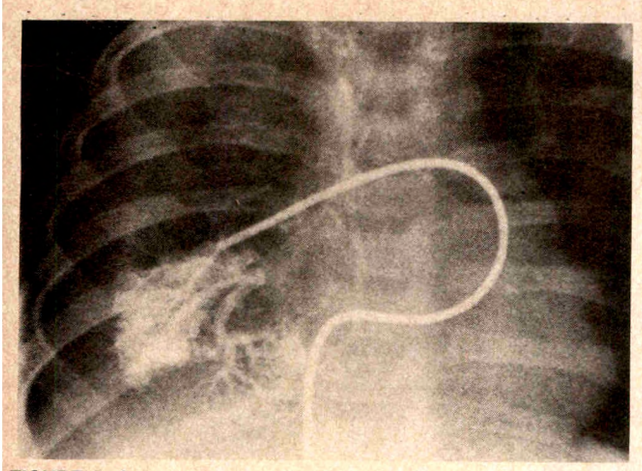

FIGURE 3. Selective wedge cineangiocardiogram of the lower lobe of the right lung revealing delayed emptying of the contrast material from the right pulmonary bed into a fine tortuous venous network. These vessels represent bronchial veins draining into the azygos vein.

Discussion

Etiology

The common pulmonary vein is a transient anatomic structure that forms as an outgrowth from the left atrium to meet with the pulmonary portion of the splanchnic plexus and the primitive cardinal and umbilicovitelline system of veins. With differential growth, this connection with the systemic circulation regresses and the four individual pulmonary veins connect with the common pulmonary vein. The common pulmonary vein is then absorbed or incorporated into the left atrium so that each of the four pulmonary veins enters the left atrium separately.[1] Imperfect development of the common pulmonary vein results in any of several distinct anatomic anomalies, the exact nature of which is determined by the degree of abnormal incorporation or obliteration of the vein into the left atrium.[2–8]

Conceptually, unilateral pulmonary vein atresia might result from an imperfect incorporation of the common pulmonary vein into the left atrium at a late stage of development, when the collateral venous channels have already regressed and are no longer available to form an anomolous pulmonary venous connection.

Bilateral obstruction of the pulmonary veins can result from abnormal development, but can also be produced by sclerosis or thrombosis, or both, of the pulmonary veins.[9,10] Bilateral pulmonary venoocclusive disease has been extensively reviewed by Rosenthal et al.[11] The pathologic hallmark of this entity is bilateral development of various degrees of obstruction of pulmonary veins and venules by thrombi[9–13] or thickening of the intima.[14–16] In our case, we observed extensive intimal fibrosis of the pulmonary veins only on the right side.

Pathophysiology

The pathophysiologic features of this case differ from those of bilateral pulmonary venous obstruction in that the obstructed right lung, in the presence of a normally draining left lung, received no obligatory pulmonary flow. Several compensatory mechanisms resulted: (1) The capacity of the pulmonary lymphatic flow was increased, as is also found in bilateral pulmonary venous obstruction.[5,6] (2) Bronchial venous blood drained from the right lung to the systemic circuit by way of dilated pleural veins converging into a large plexus emptying into the azygos vein (Fig. 3). This was interpreted as an alternative pulmonary venous pathway that evolved to bypass the obstructed pulmonary veins. (3) Pulmonary arterial blood preferentially flowed to the left lung, probably because the obstructed pulmonary venous system in the right lung could not accomodate the blood entering the pulmonary capillary bed. This hypothesis is supported by the small size of the main right pulmonary artery and by medial hypertrophy of the small pulmonary arteries (Fig. 4A). (4) Pulmonary flow to the left lung was augmented by the backward flow from the

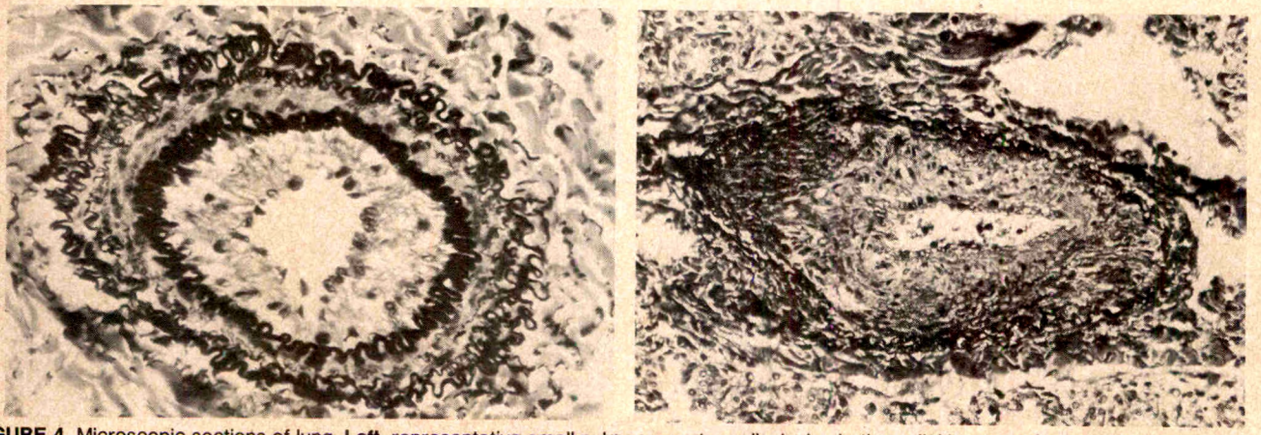

FIGURE 4. Microscopic sections of lung. **Left,** representative small pulmonary artery, disclosing both medial hypertrophy and endothelial proliferation. The outer elastic lamina is duplicated. (Verhoeff-Van Gieson elastic stain, ×460). **Right,** small pulmonary vein, disclosing intimal fibrosis, medial hypertrophy and fibrosis, and proliferation of elastic fibers in the adventitia. (Verhoeff-Van Gieson elastic stain, ×460 **(left)** and 170 **(right),** reduced by 50 percent.)

right pulmonary artery, which was supplemented by flow from the anastomoses with the bronchial artery. Evidence for such anastomoses included increased blood oxygen saturation in the right pulmonary artery, increased right pulmonary arterial wedge pressure, cineangiographic "washout" of contrast material from the periphery of the right pulmonary artery toward the main pulmonary artery and demonstration of a bronchial and pulmonary arterial connection by injection of barium after resection.

Clinical and Diagnostic Features

Our case of unilateral pulmonary venous obstruction resembled influenza, and the chest roentgenograms were initially interpreted as indicating pneumonia. Many of the radiographic shadows proved histologically to have resulted from infarcts from venous obstruction; such shadows are also found in bilateral pulmonary venoocclusive disease.[12] These recurrent infarcts produced an episodic illness characterized by pulmonary edema and hemorrhage and fever. The fever may be partially explained by the superimposed infection, which was usually slight. Subtle bacterial infection has been demonstrated in experimental ligation of pulmonary veins in dogs.[17]

The radiographic appearance of the chest was probably the most helpful diagnostic finding initially; the abnormalities were all unilateral, in contrast to those associated with bilateral pulmonary venous obstruction. They included a diffuse increase in the fine interstial and vascular markings often associated with Kerley B lines, a visible interlobar fissure, and pleural thickening or effusion, or both (Fig. 1). Isotope ventilation-perfusion studies demonstrated absent perfusion of the one lung with pulmonary venous obstruction.

The definitive diagnostic procedure in the evaluation of our patient with suspected pulmonary venous obstruction was cardiac catheterization with selective cineangiography. The increase in blood oxygen saturation in the right pulmonary artery in the absence of a patent ductus arteriosus suggested bronchial arterial communication with the pulmonary arteries. The pulmonary wedge pressure in the obstructed lung was greater than that in the nonobstructed lung. This finding correlated well with the roentgenographic findings and was produced by the small amount of obligatory flow to the obstructed lung by way of the bronchial circulation as demonstrated hemodynamically, angiographically and histologically.

Surgical correction of unilateral pulmonary venous obstruction is theoretically possible if several anatomic criteria are met. The end pulmonary venous channels must be large, out of the lung parenchyma and close to the atrial wall. In the absence of these favorable anatomic features, surgical anastomosis is impossible and pneumonectomy is recommended because the obstructed lung becomes a site of repeated infection.

Acknowledgment

We thank Miss Joyce Childress for secretarial assistance.

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Metabolic Changes in Myocardial Infarction

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Efforts to study cardiac metabolism have focused on matters of physiologic and biochemical interest; little attention has been paid to clinical applicability. At the outset, concern was with the nutrition of the heart, as first studied in the perfused cold-blooded animal and finally in the human heart in situ.[1] This phase was followed by investigations into the mechanism of coupling between excitation and contraction in heart muscle, processes related to calcium binding and uptake, and studies on the nature of contractile proteins. In addition, changes in biochemical pathways in myocardial infarction were defined and morphologic correlations accompanying the repair of myocardial infarction were described.[2]

During these phases, the clinician's interest in cardiac metabolism has been peripheral, although the fundamental importance of these studies to the clinical investigator must have been obvious. They concern the nature of disturbances underlying myocardial failure, the morphology and biochemistry of heart muscle exposed to sudden ischemia, and the development and progression and healing of a myocardial infarction.[2]

The knowledge gained has been valuable, but has failed to influence clinical thinking even though evidence has been presented showing that it is possible to increase the rate of healing of a myocardial infarction with growth hormones, catabolic steroids, ascorbic acid or insulin.[2]

From these fundamental bases, Opie, in an article in this issue of the Journal,[3] has taken a further step in relating fundamental studies on cardiac metabolism to the clinical course of patients with myocardial infarction. From a discussion of the metabolism of free fatty acids and their still doubtful relation to arrhythmias and myocardial infarction, he digresses to a discussion of the interaction between free fatty acids and catecholamines, the cellular effects of free fatty acids and the therapeutic use of glucose in heart disease. The article would have been more complete had he included observations on the link between protein synthesis, the effect of insulin, growth hormone and the repair of infarcted tissue. He stresses the concepts of Sodi-Pallares, primarily as they pertain to the prevention of cellular potassium loss. As indicated, more subtle effects of glucose-insulin-potassium mixture have been described in relating the action of insulin on protein synthesis in the infarcted area.[2] Unfortunately, in man this effect cannot be verified and in animals they necessitate difficult biochemical procedures such as the incorporation of labeled amino acids into proteins. This effect of glucose-insulin-potassium precedes by a considerable time span the other more rapid actions of glucose such as the provision of anaerobic energy to the ischemic tissue, the inhibition of lipolysis, the increase in plasma volume or the effect on the tissue content of glycogen, lactate and high energy phosphate.

I believe that the main contribution of Opie's article lies in an appraisal of the difficulties in applying results obtained "at the bench" to "the bedside." Opie has given us a scholarly discussion of the physiologic and biochemical mechanisms underlying myocardial infarction, but we must be aware that a valid translation of these results into therapy are still speculative: No Rosetta stone has yet been found. Herein lies the frustration of all of us interested in cardiac metabolism who have labored in the laboratories and have tried to apply our results to the clinic. Only too often has pure clinical judgment at the bedside alone preceded any application of fundamental scientific principles. Yet, we must continue to try to relate our academic data to the clinical situation, and eventually the stones of the mosaic may fall into place and reveal a valid and useful picture. Dr. Opie's article is a step in this direction.

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Problems in Measurement of Serum Digoxin by Commercially Available Radioimmunoassay Kits

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The rapidly expanding field of radioimmunoassay techniques has led to widespread use of this relatively simple and rapid method for determining serum digoxin concentration. Most clinical laboratories are not equipped to produce antisera and must therefore rely upon commercial sources for antibodies and radioisotopically labeled compounds. The recent proliferation of commercially available radioimmunoassay kits for measuring serum digoxin has created new and important problems for the physician and clinical laboratory.

We have tested 11 such kits (5 tritium- and 6 iodine-labeled) from nine manufacturers to assess their usefulness in measuring serum digoxin in man.[1–3] All kits were compared for: (1) precision (reproducibility of the test); (2) accuracy (recovery of a known amount of added digoxin to sera); (3) assay of serum digoxin levels; (4) specificity (analysis of the effect of digitoxin on the assay of digoxin); and (5) sensitivity (minimal detection limits of the assay).

All studies were performed in duplicate by the same operator, and the manufacturers' instructions were strictly followed. The patients' sera were free of radiation from any diagnostic procedures.[4] Our studies revealed several areas of concern.

1. Precision: The precision of the kits was evaluated by the repeated assay of two specimens for each kit. Representative samples were selected so that the digoxin level of one was 0.6 to 2 ng/ml and that of the other clearly exceeded 2 ng/ml.[1,2] Each specimen was divided into 20 aliquots and all were assayed within the same run. The coefficient of variation (the standard deviation expressed as percent of the mean) was used to describe the degree of reproducibility. The average coefficient of variation of the tritium-labeled kits was 11.1 percent (range 9.3 to 13.5 percent) at "therapeutic" levels (less than 2 ng/ml) and 7.4 percent at elevated levels (range 3.5 to 13.7 percent). The average coefficient of variation of the iodinated kits was 11.4 percent (range 1.0 to 20.4 percent) at "therapeutic" levels and 8.8 percent (range 4.1 to 19.1 percent) at elevated levels. Although overall precision as judged by the *average* coefficient of variation of all 11 kits (tritium- and iodine-labeled) was acceptable, much wider variability became evident when the iodinated kits were examined separately. Study of precision is essential because accuracy cannot be estimated when precision is poor.[5]

2. Accuracy: Table I shows the accuracy of the radioimmunoassay technique as reflected by digoxin recovery experiments with each kit. Known amounts of crystalline digoxin were added to digoxin-free sera and the samples were then analyzed for recovery. "Perfect" accuracy would have been 100 percent recovery. Values less than 100 percent would underestimate the serum digoxin level and vice versa. Accuracy in relation to the *average* amount of digoxin recovered (expressed as percent of the amount of digoxin originally added) was quite good at the various levels studied when all 11 kits were considered together, but closer analysis of the range of values revealed significant variability from kit to kit, with the iodinated kits exhibiting the most serious variations.

3. Measurement of serum digoxin: These analyses were performed using the 11 kits on sera from a small unselected patient population (Table II). Widely different results were obtained for the same sample, and there were striking differences in the number of "toxic" values (as defined by the manufacturer). Sera from a normal volunteer group (not taking cardiac glycosides) revealed essentially zero values for digoxin levels. Consequently, the discrepancies outlined in Table II would not appear to arise from a nonspecific or background effect of the sera on the assay.

The differences in the values of serum digoxin levels cannot be entirely correlated with the results of recovery experiments. Voshall et al.[6] recently pointed out that variation in individual serum samples may be related to albumin concentration, which may affect binding of the antibody supplied in the kit

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These workers demonstrated that a variation in serum albumin concentration of 1.0 g/100 ml can cause a 25 percent error in measured digoxin level. Kit to kit variability may stem from other sources: Smith and Haber[7] have emphasized the problems of low affinity antisera, inadequate quality control and purity of the digoxin assay standards as potential sources of poor precision and accuracy. The better performance of tritium-labeled digoxin kits may be partially attributed to technical factors since all of the method of these kits was basically the same, whereas that of the iodinated kits differed substantially (mostly in the technique employed for separating free and antibody-bound digoxin). The possible inconsistent reliability and stability of the currently available iodinated digoxin has been discussed by Drews and Pileggi[8] as another possible critical source of error in digoxin radioimmunoassay. Troublesome iodinated digoxin may come from potentially impure ^{125}I supplied by radiochemical manufacturers.[9] More studies are required to further standardize the assay for serum digoxin by means of radioimmunoassay kits.

4. Specificity: All 11 kits showed the anticipated effect of digitoxin on the assay of digoxin. For example, the addition of 20 ng/ml of digitoxin to drug-free sera resulted in digoxin levels ranging from 0.61 to 2.4 ng/ml with the iodinated kits.[2] As previously reported,[10] caution is needed when assaying for digoxin when the actual glycoside ingested is unknown.

5. Sensitivity: Only one kit could accurately differentiate a digoxin concentration of 0.1 ng/ml from zero and only one could accurately differentiate a concentration of 0.2 ng/ml from zero.[3] None of the other kits could distinguish 0.3 ng/ml from zero.[3] These limitations are important because sera from normal volunteers (laboratory personnel) not receiving digoxin or other cardiac glycosides may occasionally reveal spurious but consistently low serum digoxin levels.[1,2] Indeed, we found that with most kits a digoxin level of 0.2 or 0.3 ng/ml cannot be interpreted as evidence of previous digoxin or digitoxin therapy. Conversely, a zero digoxin level does not rule out the presence of a relatively small but finite amount of digoxin in the serum. The minimal detection limit of most currently available digoxin radioimmunoassay kits appears to be 0.5 ng/ml.[3]

Clinical implications. Each laboratory must carefully and rigorously evaluate its own digoxin radioimmunoassay kit before using it as a routine diagnostic tool. Key measurements should include tests of precision and accuracy to evaluate the method and reagents. Adequate quality control within studies and from day to day are mandatory. Ongoing checks of commercially available material are recommended even if the initial evaluation of a kit is acceptable because antisera, tracers and assay standards may vary significantly from lot to lot. Each laboratory should

TABLE I

Accuracy of Commercially Available Digoxin Radioimmunoassay Kits: Recovery Experiments[1,2]

Type of Commercial Kit	Number of Kits Evaluated	Digoxin Added* (ng/ml)	Digoxin Recovery (%) Average from All Kits	Digoxin Recovery (%) Range from Individual Kits
Iodine-labeled	6	0.5	85	12–122
		1.0	100	69–127
		2.0	101	78–113
		5.0	94	73–104
Tritium-labeled	5	0.5	91	78–98
		1.0	91	83–107
		2.0	97	89.5–108.5
		5.0	104	86–120

* Purchased from Schwarz/Mann, Orangeburg, N.J.
The recovery data are based on a minimum of four experiments at each level.

TABLE II

Analysis of Digoxin in Patient Samples (ng/ml)[1,2] *

Kit	Patient Sample 1	2	3	4	5	6	7	8	9	10	Samples with "Toxic" Results† (mean no.)
A. Iodine-Labeled Kits											
A	0.1	0	0.8	0	1.5	2.0	2.9	2.3	2.9	2.3	4
B	1.5	0.6	2.0	0.2	2.1	1.8	3.9	3.3	3.7	4.1	5
C	1.0	0.6	1.7	0	1.9	1.8	4.1	3.1	3.8	4.9	4
D	1.2	0.9	1.7	0.6	2.2	2.2	3.9	3.1	3.4	3.9	6
E	0.4	0	1.5	0	1.8	1.2	4.5	3.3	3.0	2.8	4
F	0.7	0.4	0.9	0.1	1.6	1.1	1.8	1.8	2.2	2.0	1
B. Tritium-Labeled Kits											
G	2.9	4.8	4.2	3.5	0	1.3	1.1	0.6	1.9	0.9	4
H	2.2	3.2	2.8	2.8	0	0.7	0.8	0.1	0.9	0.5	4
I	2.1	3.0	2.4	2.4	0	0.9	0.9	0.6	0.7	0.5	4
J	2.0	3.9	2.5	3.3	0	1.3	1.3	0.8	1.5	0.5	4
K	2.7	4.5	3.6	4.6	0	1.3	1.3	0.4	1.7	0.5	4

* Kits A to F employed iodinated tracer and all assayed the same samples. A different group of samples was assayed by the tritium-labeled kits, G to K.
† According to literature supplied by manufacturer.

determine its own "therapeutic" and "toxic" digoxin values in conjunction with the local clinical experience. When comparing data from different laboratories one must know which kit has been used because variations in values from the same sample may be due to differences in the kit rather than in technique itself. In this context it should be remembered that the diagnosis of digitalis intoxication is a clinical, never a laboratory, diagnosis.[11] The clinician should appreciate the pitfalls and limitations of this recently available test in order to use it wisely in managing patients with heart disease.

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DYSKINESIA OF LEFT VENTRICLE IS A MISNOMER

Recently left ventricular wall motion has been described in many terms such as akinesia, hypokinesia or dyskinesia. Dyskinesia is often used to refer to left ventricular aneurysm characterized by paradoxical motion. During systole the left ventricle normally moves uniformly toward the central axis and the apex toward the base of the heart. But in true ventricular aneurysm, the aneurysmal portion is supposed to move away from the base like a rubber balloon—when one part is squeezed the rest bulges out—hence, the term dyskinesia or paradoxical motion. However, on examination of a left ventriculogram during systole, the aneurysmal portion, instead of moving away paradoxically as it is said to, remains motionless and the rest of the wall moves toward the central axis. Although I have reviewed more than 200 left ventriculograms of cases of true aneurysm, all documented at operation, I have not observed the paradoxical motion. Paradoxical motion was not seen even during surgical exposure of the aneurysms.[1] Histologic studies of the aneurysm in all cases revealed the tissue that comprises the aneurysm to be fibrous tissue, which lacks elasticity. Therefore, we should not expect the aneurysm to have paradoxical motion.

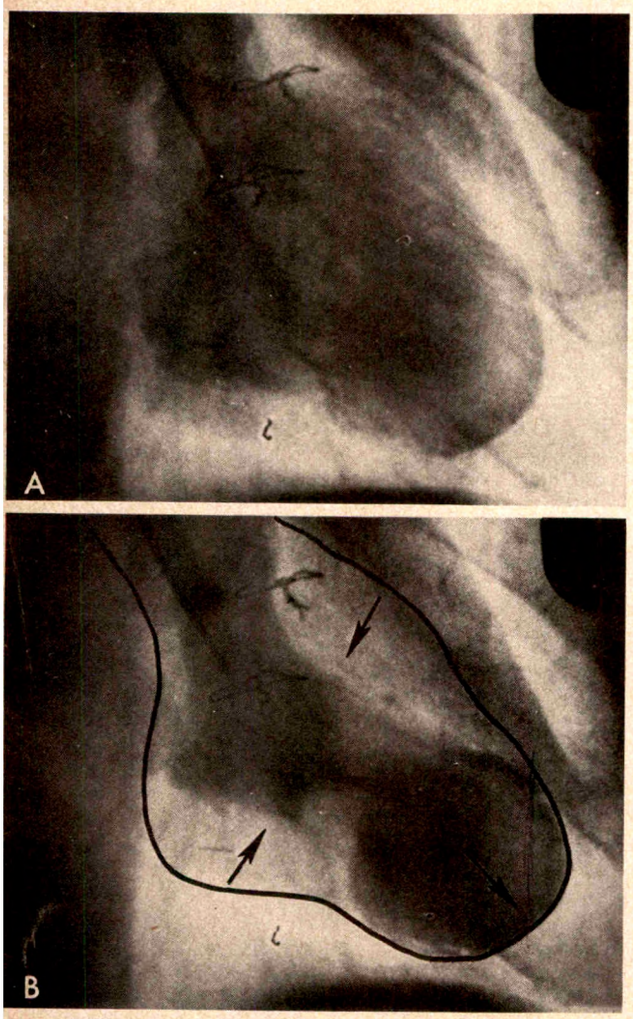

FIGURE 1. Left ventriculogram of a patient during diastole **(A)** and during systole **(B)**. Line shows superimposition of diastole shown in **A. Inward arrows** show the direction of motion of the heart muscle. At the apex the **arrow** shows the supposedly outward motion of ventricular aneurysm. Note the exact position of the ventricular aneurysm during both systole and diastole.

The term dyskinesia was probably used by early roentgenologists viewing the heart wall motion during conventional fluoroscopy. Paradoxical motion of the left ventricle may be an optical illusion. However, the left ventriculogram overcomes that illusion, probably because of improvement in modern image intensification methods and television monitors. Because dyskinesia of the left ventricle does not occur, the use of this term should not be condoned.

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Reference

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CONCEALED VENTRICULAR EXTRASYSTOLES

Lee et al.[1] recently discussed their experimental observations with concealed ventricular extrasystoles. This interesting phenomenon has been virtually ignored since the original reports by Schamroth and Marriott[2,3] in 1961 and 1963, although Schamroth considers it a common disorder of rhythm.[4]

Lee et al. constructed an experimental model with a continuous and persistent bigeminal ectopic mechanism. By decreasing the coupling interval between conducted and ectopic beats, they produced true concealment with only odd number conducted beats intervening between extrasystoles. To explain quadrigeminy, they proposed the mechanism of cyclic alterations in refractory period prolongation proportional to the length of the preceding cardiac cycle, with concealed extrasystoles following longer compensatory pauses and manifest extrasystoles following shorter consecutive conducted beat cycles. A cumulative effect refractory period prolongation was hypothesized to explain mixed bigeminy and quadrigeminy. The reason for longer periods of concealment (5 to 13 uninterrupted conducted beats) was more difficult to explain.

I recently reported a previously unobserved phenomenon, concealed extrasystolic ventricular bigeminy with interpolation.[5] In this arrhythmia, there are no compensatory pauses and the mechanism of longer cycle lengths with resultant prolongation of the subsequent ventricular refractory period cannot be evoked to explain concealment. Moreover, the appearance of extrasystoles obeyed the "rule of bigeminy"[6] with longer cycle R-R intervals precipitating

and shorter cycle R-R intervals not precipitating manifest extrasystoles. This, too, is at variance with the hypothesis of Lee et al., and would favor ectopic enhancement rather than reentry as the cause of coupled extrasystoles.[1,4] Only an even number distribution (2, 4 or 8) of conducted beats intervened between extrasystoles conforming to 2n + 2 sinus beats between manifest extrasystoles during a continuous recording of 5 minute's duration with 108 interectopic intervals. Schamroth and Marriott[3] have also reported a case of concealed trigeminy with interpolation with 3n + 3 sinus beats between extrasystoles.

I would be interested if Lee et al. could reconcile the apparent contradictions between my observations and their results.

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REPLY

As Dr. Lightfoot has emphasized, the entire subject of concealed extrasystoles has been neglected, although it now appears that this type of rhythm disturbance is very commonplace. Dr. Lightfoot's paper[2] on concealed bigeminy with interpolation is now in press. We also have a paper in press describing three variants of concealed bigeminy, one of which is also concealed bigeminy with interpolation.[3]

In our recent study[1] of concealed bigeminy in animals, we demonstrated that one mechanism producing concealment was the prolongation of refractoriness associated with the compensatory pause. In that study and in our current clinical study,[3] we described other possible mechanisms as well. In both papers, we favored the reentry over the ectopic enhancement theory as an explanation for the general phenomenon, but we did acknowledge that definitive proof has not yet been obtained. Dr. Lightfoot indicates that the appearance of extrasystoles in his patient obeyed the "rule of bigeminy." He cites this as support for the ectopic enhancement rather than the reentry theory. However, Langendorf et al.[4] who formulated the "rule of bigeminy," concluded that their rule strongly favored the reentry theory: "The fact, as shown in this report, that the occurrence of a premature systole may be a function of cycle length is hard to reconcile with any other explanation but the re-entry concept."

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SIGNIFICANCE OF FOURTH HEART SOUND AND SPLIT FIRST HEART SOUND

Recently increased attention was given to the fourth heart sound, and the discussion provoked by the editorial of Fowler and Adolph[1] revealed many different views.[2,3] One of the main problems is an auscultatory and phonocardiographic interchange between the fourth heart sound and the split first heart sound. Fowler and Adolph[2] concluded: "Many instances of reported audible fourth sounds by students, house staff and others actually represent an audible split of the first sound. We welcome further studies to prove or deny this hypothesis." This challenge has stimulated us to communicate our experiences and to call attention to an incidental relation of the split first heart sound to the fourth sound.

Many investigators[1–5] have not stressed the difference between physiologic (close) and pathologic (wide) splitting of the first sound nor have they stressed the importance of the pathologic splitting of the first heart sound. However, Rectra et al.[3] found that of 57 patients with cardiovascular abnormalities and with the fourth sound verified by a phonocardiogram, 16 had splitting of the first sound (28 percent) and of 20 patients with cardiovascular abnormalities with no fourth sound, 16 (80 percent) had splitting of the first sound. Recordings suggest that some of these patients probably had pathologic splitting of the first heart sound. Such a distribution of the split first sound could have a clinical significance.

Our observation concerns patients in functional classes I and II (New York Heart Association criteria) (diagnosis: chronic ischemic heart disease, hypertensive heart disease and cardiomyopathy, 40 subjects, age range 26 to 77 years, average age 51.3 years). All patients had a regular sinus rhythm. Disturbances of atrioventricular (A-V) conduction and bundle branch block were absent. In these patients the first sound was widely split, its duration was longer and of smaller amplitude in comparison with the normal first sound, which on auscultation was soft and muffled. Sounds with normal or increased amplitude were also recorded (on auscultation loud or accentuated split first sound). All pathologic splittings of the first sound were audible and were confirmed phonocardiographically. Average duration of the split was 70 msec. The occurrence of the wide first sound splitting was reported by Cossio et al.[6] and recently in patients with chronic coronary heart disease without cardiac failure.[7] In all except three patients, abnormal systolic time intervals (prolongation of preejection period [PEP], abbreviations of left ventricular ejection time [LVET] and increase of PEP/LVET ratio) were recorded. In randomly selected healthy persons or patients in whom cardiopulmonary disease was excluded (28 subjects, age range 21 to 95 years, average age 42.8 years) only physiologic splitting of the first sound and normal systolic time intervals were found. All differences discussed were statistically significant (P <0.01–0.001). Observed auscultatory and phonocardiographic changes of the first heart sound accompanied by abnormal systolic time intervals could be

explained by left ventricular dysfunction.

It seems that the fourth sound (eventually the third sound) could be connected with abnormalities of the first sound by a common denominator: Simultaneous occurrence of the audible fourth and third sounds was found only in the patients with heart disease and not in the control group. In addition we recorded an occurrence of the pathologic first sound splitting at the initial phase of cardiac insufficiency before appearance of the fourth (eventual third) sound. When blood flow was restored, splitting of the first sound disappeared simultaneously with or just after the fourth sound. Auscultatory and phonocardiographic disappearance of the diastolic sounds and normalization of the first sound during left ventricular compensation of acute myocardial infarction, hypertensive heart disease, cardiomyopathy or chronic ischemic heart disease can hardly be regarded as accidental.

Data given by other authors support our views. Duchosal[8] suggested a close and probably causal relation between the fourth sound and alterations of the first sound. In hypertensive patients he recorded phonocardiographically a longer duration of the first sound (150 msec) preceding decompensation. The first heart sound prolongation was audible and considered a precursor of atrial gallop. Master and Friedman[9] found that of patients with acute myocardial infarction who had a muffled first sound and a fourth sound, 96 percent had cardiac failure; manifest circulatory failure was found in only 33 percent of patients without a decrease of the amplitude of the first sound.

Our experience suggests that (1) a true audible fourth heart sound is usually a pathologic finding; (2) auscultatory splitting of the first sound often mimics the fourth sound; (3) the fourth sound with the first component of the first sound could simulate the splitting of the first sound; and (4) alterations of the first sound, mainly wide splitting, in patients with cardiovascular diseases in whom valvular damage is excluded and A-V and ventricular conduction is within normal limits should be considered a sign of disturbed left ventricular dynamics. In such cases wide splitting of the first sound could precede the appearance of the fourth sound or third sound, or both, and could be a sign of incipient cardiac insufficiency.

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REPLY

Riecansky and Haviar may be correct in their contention that increased width of splitting of the first heart sound may be a sign of heart disease, and that the sign often precedes the development of audible third and fourth heart sounds when there is progressive left ventricular dysfunction. Our editorial[1] dealt with splitting of the first sound in normal subjects only; we have no data concerning splitting of the first sound in heart disease. As we have emphasized, it is essential to distinguish between sounds that are recorded by phonocardiogram and those that are actually audible with the aid of the stethoscope. We suggest that Riecansky and Haviar submit their material for publication so that it may be subjected to critical scrutiny.

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BOARD CERTIFICATION OF CARDIOLOGISTS

We were particularly struck by the finding of Pritchard and Abelmann[1] that only 10 percent of cardiologists are certified in their subspecialty and were disappointed that nothing was recommended for the improvement of this situation. Of course, with time this percentage will increase as new graduates of the present residency programs practice cardiology in increasing numbers.

We would like to suggest a recommendation, with ourselves as examples. We are clinical cardiologists, according to definition. We are board-certified in Internal Medicine and one of us has just taken the recertification examination. We have practiced cardiology for 5 and 10 years, respectively (over 70 percent), are accepting new patients only by doctor's referrals for cardiac problems and are actively involved in cardiology in two hospitals, including one major medical center. We have made great attempts to keep up with the advances in the field. However, we are ineligible to take the examination in the subspecialty because we did not spend the prerequisite time in a formal residency program limited to cardiology. We are sure there are vast numbers of clinical cardiologists in this same position and are equally certain that many of us could be certified if given the opportunity. We recall that, in the not too distant past, the board examination in Internal Medicine was offered to internists who lacked the prerequisite number of years of formal residency and that subsequently many passed who are presently very competent board-certified internists. We suggest that clinical cardiologists such as ourselves be offered a similar opportunity to become board-certified cardiologists by taking the tests.

Calvin E. Oyer, MD
Lubomir Jawny, MD
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Reference

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REPLY

Those of us engaged in the Adult Cardiology Manpower Study[1] were truly surprised to find that only 55 percent of

all cardiologists are certified in Internal Medicine, and only about 10 percent are certified in Cardiovascular Disease. Even in the case of the younger cardiac specialists who are the product of more formal training, require special skills or expertise and are more apt to see patients in consultation, the percentage certified in Internal Medicine and the percentage certified in Cardiovascular Disease were not much higher. The real question is, are these current findings in the best interest of the patient? How can the patient determine that the doctor caring for his cardiovascular problem is qualified to do so?

The American Board of Internal Medicine and its Subspecialty Board in Cardiovascular Disease, as is true for other boards, have established rather rigid criteria for training. It is true that in the past an internist without the required training could, after a number of years of practice, be admitted to examination and, if successful, certified. Thus far, the American Board of Internal Medicine has maintained a rather rigid attitude about reverting to "suboptimal training program" prerequisites for applicants. However, the board is aware of the pressures to face this issue that will develop in the future as recertification becomes necessary. The American College of Cardiology, in conjunction with the Council of Clinical Cardiology of the American Heart Association, has established a dialogue with the Subspecialty Board for the purpose of developing a mechanism for recertification of certified cardiologists. Preliminary discussions indicate that the self-assessment examination recently prepared by the College and the American Heart Association will serve the same purpose as the self-assessment examination for internists that was prepared by the American College of Physicians.

The American College of Cardiology is mindful of the large number of cardiologists who are not certified but who are practicing as cardiologists. Many are outstanding cardiologists, others are probably general internists and would more correctly be referred to as having interests in cardiology.

We appreciate the problem presented by Oyer and Jawny and assume that in the not-too-distant future some solution will be made that takes into account their situation, which appears to be a general one.

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CORONARY HEART DISEASE, 2nd International Symposium at Frankfurt 1972, edited by K. Kaltenbach, P. Lichtlen and G. C. Friesinger. Stuttgart, Germany, Georg Thieme, 1973, 329 pages, $26.70

This symposium consists of seven sections: (1) action of nitroglycerin, experimental and clinical findings; (2) coronary arteriography and ventriculography; (3) the course of coronary artery disease evaluated by coronary angiography; (4) the left ventricle in coronary disease; (5) measurement of left ventricular volume; (6) surgical treatment of left ventricular failure in coronary disease; and (7) surgery of coronary arteries. The investigations reported in these various sections are usually of 4 to 7 pages, appropriately illustrated and summarized and provided with pertinent references.

The section on nitroglycerin contains a sufficiently lengthy and detailed summary of the cardiovascular effects of this drug to make it of value as a source of reference material for investigators. The section on coronary arteriography reviews experiences with the Sones and Judkins techniques, tabulating and comparing data on complications. Perhaps surprisingly, the section devoted to the course of coronary disease, as evaluated by coronary arteriography, has not been superseded to any great extent. Studies of the maximal rate of decline of left ventricular pressure and relaxation of velocity of the contractile elements during myocardial ischemia highlight the section related to the left ventricle in coronary disease. Description of an automated method for calculating left ventricular volume and a report of utilization of scintillation cameras for the noninvasive measurement of left ventricular volume are featured in the section on ventricular volume. Means of assessing aortocoronary bypass, such as intraoperative angiocardiography, electromagnetic flowmetry and xenon residue techniques, are included in the section on coronary surgery.

The book is spotty. It may be of value to physicians with specific requirements for detailed information in the areas covered by the various sections.

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SICK SINUS SYNDROME, by M. Irene Ferrer, MD, New York, Futura Publishing Company, 1974, 122 pages

It has been 30 years since this reviewer, then a medical student, was first exposed to the medical talents of Dr. Irene Ferrer, and almost 25 years since he was a cardiology fellow in the catheterization laboratory under her. This volume demonstrates that the years have done nothing to alter her ability to analyze incisively medical problems and develop appropriate therapeutic approaches. The book also demonstrates that a knowledge of clinical electrophysiology has become essential to the clinical cardiologist and electrocardiographer and illustrates the importance of clinically useful methods for evaluation of the conduction system.

This short volume provides the student of cardiology with an excellent review of the present status of the sick sinus syndrome that can easily be read in one evening. The clinical and electrocardiographic features of the syndrome are clearly presented, with emphasis on primary sinus bradycardia, sinus arrest and sinoatrial exit block. The brady-tachyarrhythmia sequence is discussed with clarity, the frequency of associated atrioventricular conduction disturbances is stressed as well as the need for careful observation and possible clinical study of patients with sinus

bradycardia with heart rates below 50 beats/min, especially if the rates are in the high 30's or low 40's.

The section on provocative tests for diagnosis of this syndrome is especially valuable. Since the electrocardiographic manifestations may be intermittent, long-term (10 to 24 hour) electrocardiographic tape monitoring may be needed. If these tape studies are noncontributory, then the responses to intravenous administration of atropine and isoproterenol may be useful. Atropine is administered in 1 to 2 mg doses; if the sinus rate fails to increase, usually to 80 to 90/min, the diagnosis of sick sinus syndrome should be suspected and the possibility of vagotonia decreased. Isoproterenol is used as a sinus node generator stimulus. However, right atrial pacing with overdrive suppression is the best and most useful laboratory test for the sick sinus syndrome. Dr. Ferrer stresses that drugs *alone* are often not useful, and that ventricular pacing is the preferred therapy. She emphasizes that optimal clinical timing of permanent ventricular pacer implantation is often quite difficult.

A minor criticism is the lack of discussion of the possible use of coronary sinus pacing in preference to right ventricular pacing, but only if His bundle studies have established that atrioventricular conduction is normal. The author also fails to discuss the occasional atrial pacing study wherein sinus nodal recovery time is normal before administration of atropine but becomes abnormal after atropine. This phenomenon is due to atrio-sinus block during atrial pacing before atropine; a prolonged sinus recovery time (500 msec longer than the control sinus cycle interval) after atropine suggests strongly the sick sinus syndrome.

The volume is highly recommended to the physician interested in a common clinical problem.

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PATHOLOGY ANNUAL: 1974, edited by Sheldon C. Sommers. New York, Appleton-Century-Crofts, 1974, 478 pages, $20.50

Advances in the field of pathology should be of general interest to all physicians, but only three chapters in this volume have particular significance for the specialist in cardiovascular diseases.

The pathologic features of chronic pulmonary hypertension are reviewed by Jesse Edwards, whose experience in this area is legendary and who presents classic background material. Differentiation of the various pathologic lesions in relation to the different types of intracardiac shunts is of primary importance to the student of cardiology, but unfortunately, there is a paucity of current references on this topic. The pathophysiologic features of pulmonary hypertension, particularly the dynamic relation to many diverse clinical states and ventilatory patterns, have received much recent attention. Some correlation of these data should have been provided in an annual review.

The chapter on sarcoidosis adds 4 cases with detailed cardiac pathologic data to the 118 reported autopsy cases. Discussion of the pathophysiologic features of the various lesions, particularly of the conduction system, and their clinical significance is informative.

The section on the conduction system by Lev and Bharati beautifully documents and illustrates normal anatomy, histology and pathology in a lucid and graphic way. The anomalous nature of the conduction system in various congenital defects as well as the specific pathologic lesions in various diseases is included. Some correlation of lesions with electrocardiographic studies and His bundle electrograms is attempted. Most helpful is the extensive bibliography with 194 cited references.

The lucidity of the text and the accompanying illustrations of both microscopic and gross anatomy is further enhanced by graphic diagrams of the anatomic structures of the conduction system. These features should be helpful to the cardiac surgeon selecting a surgical approach and technique as well as to the clinical cardiologist involved in the diagnosis and management of rhythm and conduction disturbances.

Although the volume as a whole might not be indispensable to the cardiologist's library, its sections on the anatomy and pathology of the conduction system of the heart make it a useful reference.

Alfred J. Kaltman, MD
New York, New York

President's Page: New Orleans 1976

Unfortunately, dichotomous thinking concerning the roles of the various participants in our health care delivery system has led all too frequently to adverse attitudes within the system itself. For example, as much as we would like to deny the existence of such undercurrents, antagonisms between researcher and practicing physician, the "ivory tower" people and the "life-is-real" group, do become apparent on occasion, mostly through innuendo.

For the most part cardiology has not been afflicted with the divisionary disease and, therefore, it may be unnecessary or even unwise to focus on it. However, to emphasize the unity of purpose and the interdependence of the various disciplines within cardiology, we have chosen as the theme for the 25th Annual Scientific Sessions, New Orleans, February 23–26, 1976: *Research and Patient Care—The Continuum.*

In accordance with the theme and to emphasize further the continuous, homogeneous and the fundamental common character of our activities as members of the American College of Cardiology, the program includes symposia such as "From Laboratory Concepts to Bedside Clinical Application." In this symposium, investigators who proposed concepts that ultimately proved to make a significant contribution to our knowledge will present their original papers or discuss the origin of the concept; they will be followed by clinicians discussing the present day application to clinical cardiology of the original concept or innovation. The *Core Curriculum* entitled "From the Laboratory To The Bedside" will focus on recent advances in clinical cardiology based on newer physiologic and biochemical knowledge. There will be symposia updating developments in coronary care, treatment of the postoperative and hypertensive patient, exercise testing and the computer in electrocardiography. As usual, the abstract sessions and special sessions on problems in investigative and clinical areas, such as the importance of clinical subsets in the selection of patients for coronary revascularization, the timing of cardiac valve replacement and evaluation of ventricular dysfunction, will provide the foundation for better patient care in the future.

I am convinced that the Scientific Program Committee, under the leadership of Drs. Suzanne B. Knoebel and Borys Surawicz, Co-Chairmen, has provided Annual Scientific Sessions worthy of being our 25th. It is, once again, a clinically oriented but scientifically based program with full recognition of the contribution of all to the advancement of cardiology.

With the recent emphasis by the College on evaluation of educational methods, the Annual Scientific Sessions have come under rigorous scrutiny. The consensus has been that the sessions provide in a compact format an educational opportunity unique in faculty as well as in quality and quantity of material presented. The learning environment created at the national meeting lends itself to a relatively easy acquisition of ideas, concepts and facts. This year we have an added bonus, namely, the City of New Orleans itself, coupled with the superb arrangements made by Dr. and Mrs. Allan Goldman. See you all in New Orleans!

Charles Fisch, MD, FACC
President
American College of Cardiology

New Members

The following were also elected to Associate Fellowship in the American College of Cardiology on May 22, 1975: Juan J. A. Cosentino, MD, Argentina; and Anthony Marlon, MD, Nevada.

The following group of Associate Fellows were elected on July 28, 1975:

Protasio L. DaLuz, MD, California
John J. Fenoglio, Jr., MD, Washington, DC
Edilberto G. Gozo, Jr., MD, Philippines
Soon Gan Ng, MD, Malaysia
Vincent J. Proskey, MD, Missouri
Kuddythamby Sinnathamby, MD, Ohio
Peter Torbey, MD, Michigan
Bernardo Treistman, MD, Texas

Vidya S. Kaushik, MD, California, and Mario Trivellato, MD, Italy, were elected Affiliates on July 28, 1975.

The following individuals were elected to membership in the American College of Cardiology on September 28, 1975, in the category indicated.

Fellowship

AHMAD, Masud, MD, Oregon
AMRAM, Salomao S., MD, Portugal
BERBERICH, Stephen N., MD, California
BEYDA, Ezra J., MD, Illinois
BONCHEK, Lawrence I., MD, Oregon
BOST, Charles R., MD, Pennsylvania
BROWN, David F., MD, New York
BRUSCA, Antonio, MD, Italy
COBB, Tyson C., MD, California
COHEN, Morris, MD, Florida
CONNER, Paul K., Jr., MD, Texas
COOKSEY, Jon D., MD, Missouri
CRAVER, Joseph M., MD, Georgia
CRETICOS, Angelo P., MD, Illinois
CUETO-Garcia, Luis, MD, Mexico
DAILY, Pat O., MD, California
DANGEL, James C., MD, Massachusetts
DAS, Jadunath P., MB, BS, India
EDELSTEIN, Josef, MD, Ohio
ENRIGHT, Lee P., MD, California
FORTE, Anthony L., MD, Arizona
FRIEDMAN, Joel P., MD, California
GARFEIN, Oscar B., MD, New York
GILLETTE, Paul C., MD, Texas
GILLILAND, J. Campbell, MD, Arkansas
GOLDBARG, Alberto N., MD, Illinois
GOOTMAN, Norman L., MD, New York
GREENFIELD, Lazar J., MD, Virginia
GUNTON, Ramsay W., MD, Canada
HALLIDIE-Smith, Katherine A., MB, BS, England
HALPERN, Barry L., MD, Florida
HAMZAVI, S. A., MD, Pennsylvania
HARTSTEIN, Marvin L., MD, New York
HEGDE, K. Kushala, MD, Ohio
ISCH, John H., MD, Indiana
ISHIKAWA, Kyozo, MD, Japan
IYENGAR, N. V. Ramanuja, MD, Florida
JAMIL, Mohammad, MD, Illinois
KAHN, Alan R., MD, Minnesota
KAUFMAN, Steven K., MD, District of Columbia
KEARNEY, Donald J., MD, Pennsylvania
KIM, Yeong Ho, MD, Illinois
KING, Harold, MD, Indiana
KLOCKE, Francis J., MD, New York
LARAGH, John H., MD, New York
LEVITT, Barrie, MD, New York
LESTER, F. Martin, MD, Alabama
LONDE, Stephen P., MD, California
McGOON, Dwight C., MD, Minnesota
McLEAN, Charles E., MD, Connecticut
MAILHOT, James, MD, California
MARCUS, Melvin L., MD, Iowa
MARRASH, Samir E., MD, Connecticut
MELDRUM, D. A. N., MD, Canada
MENON, Vijayan A., MD, New York
MERCER, Charles W., MD, Alabama
MILLER, Joseph I., Jr., MD, Georgia
MILLER, Charles L., MD, New Jersey
MYERBURG, Robert J., MD, Florida
NARAYANAN, Col. G. R., MD, India
NATHANSON, Michael, MD, California
OCKENE, Ira S., MD, Massachusetts
O'DONOGHUE, J. Kevin, MD, Illinois
ORISCELLO, Ralph G., MD, New Jersey
PARK, Myung K., MD, Kansas
PARKE, C. W. Kelly, MD, Ohio
PASTERNAC, Andre, MD, Canada
PECKHAM, Gerald B., MD, Canada
PEREZ-Martinez, Victor M., MD, Spain
PIGFORD, Robert T., MD, North Carolina
POPIO, Kenneth A., MD, New York
POPOVSKY, Julio, MD, Ohio
POST, Martin R., MD, New York
POTANIN, Constantine, MD, Tennessee
QUINONES, Miguel A., MD, Texas
RICHTER, Henry S., MD, New York
ROEDER, Robert E., MD, Kansas
ROELANDT, Jose R. T. C., MD, The Netherlands
RUTHERFORD, Barry D., MD, Minnesota
SABBAGH, Adid H., MD, Arizona
SALINAS-Madrigal, Luis, MD, Mexico
SCARANO, Victor R., MD, Florida
SCHERLAG, Benjamin J., PhD, Florida
SCHWEITZER, Pavol, MD, New Jersey
SEGAL, Herman B., MD, District of Columbia
SETHI, Surendra K., MD, Pennsylvania
SHAVER, Verne C., MD, Pennsylvania
SILVERSTEIN, Bernard S., MD, Florida
STEINHOUSE, Kenneth M., MD, New Jersey
STRANG, John E. MD, Pennsylvania
SUTTON, Richard, MD, England
TEICHHOLZ, Louis E., MD, New York
TIMMAPURI, Abdul N., MD, New Jersey
TRESCH, Donald D., MD, Wisconsin
TRISTANI, Felix E., MD, Wisconsin
TURVEY, B. Edward, Jr., MD, Colorado
ULLYOT, Daniel J., MD, California
VAULES, David W., MD, New York
VEDAM, Venkata S., MD, Illinois
VENKATARAMAN, K., MD, California
WOLFF, Grace S., MD, New York
WHITE, Carl W., MD, Iowa
ZAKHEIM, Richard M., MD, Kansas
ZAJTCHUK, Rostik, MD, Colorado

Advanced to Fellowship

ADAMS, Willard P., MD, California
ANDERSON, Gary J., MD, Pennsylvania
BARROW, Mark V., MD, Florida
BEASLEY, Haley Kent, MD, Texas
BERTUCCI, Joseph P., MD, Michigan
BYRNE-Quinn, Edward, MD, Arizona
COLANDREA, Michael A., MD, Illinois
CONDE, Cesar A., MD, Florida
CUTARELLI, Renato, MD, Ohio
DAVIES, Richard O., MD, Canada
DOUGLAS, John E., MD, Arkansas
GILLIE, Edward, MD, New York
GRABER, John D., MD, Washington
HAMMILL, William A., MD, South Carolina
HARRISON, Hall E., MD, Kansas
HEBBAR, Satya N., MD, Kansas
HOLLAND, William E., MD, Virginia
KARP, Robert B., MD, Alabama
LUND, Harold G., MD, California
MERCER, Edward N., MD, Canada
MILLER, Alan B., MD, Florida
PARAMESWARAN, Ramalingaier, MD, Pennsylvania
ROSEN, Michael R., MD, New York
STRICKLAND, Avery W., MD, Georgia
WAYNE, Howard N., MD, California
WINDOM, Robert E., MD, Florida
ZENER, Julian C., MD, California

Associate Fellowship

BAGA, Victor B., MD, Florida
BOPITIYA, Chandana, MD, New York
COHEN, Larry S., MD, Florida
FOX, William, MD, North Carolina
FRANK, Martin J., MD, District of Columbia
GANN, Dietmar, MD, Florida
GEDDES, John S., MD, Northern Ireland
GIBSON, Milton E., MD, Indiana
GULATI, Ravindra B., MD, India
HALLORAN, Randolph M., MD, Virginia
HATTENHAUER, Mark T., MD, Oregon
HYLEN, John C., MD, Idaho
KUNSTADT, Dorothy, MD, New York
LATTIN, Gary M., MD, Pennsylvania
LIM, Chin Hock, MD, Singapore
MELLER, Jose, MD, New York
MITAL, Mohan S., MD, Pennsylvania
MYER, Brij N.S., MD, Texas
OWENS, William C., MD, Idaho
PALANK, Edward A., MD, New York
RASHID, Ahmad, MD, Florida
RODRIGUEZ-Gilabert, Cesar, MD, Mexico
SAHA, Asis K., MD, Florida
SAPPINGTON, Joseph B., MD, Connecticut
SCHANG, Steven J., Jr., MD, Florida
SCHWADE, Jack L., MD, Texas
SINNO, Mohamed Z., MD, Illinois
WOLTHIUS, Roger A., PhD, Texas
YOON, Myung S., MD, New York
ZUREIKAT, Lt Col Harran, MD, Jordan

Advanced to Associate Fellowship

BAMRAH, Virinderjit S., MD, Wisconsin
KHAN, Abdul H., MD, Rhode Island
KUCINSKI, Chester S., MD, Colorado

Affiliate

ABDULLA, Abdulla M., MD, Georgia
AWDEH, Mahir R., MD, Texas
CAMM, A. John, MD, Vermont
CANEDO, Mario I., MD, Georgia
CLARK, Cecil W., MD, Louisiana
DURAIRAJ, S. K., MD, California
FARAHANY, Hossein H., MD, South Carolina
FRAGOSO-Marmolejo, Javier, MD, Mexico
HILDRETH, John A., MD, Florida
HONG, Chong K. Michael, MD, Illinois
IRARRAZAVAL, Manuel J., MD, Ohio
KANSAL, Santosh S., MD, Alabama
KOPPES, Gerald M., MD, Texas
LAMOREAUX, LeRoy F., MD, Oregon
LASKA, Edward M., MD, Pennsylvania
MANISCALCO, James, MD, California
MOTA-Lemus, Javier, MD, Mexico
QUIROS-Rivera, Jose Antonio, MD, Panama
RAMIREZ-Quintero, Jose A., MD, Mexico
TANPRASERT, Pravit, MD, Illinois

CANDIDATES CERTIFIED

Candidates Certified by the American Board of Pediatrics, Inc., Sub-Board of Pediatric Cardiology

May 1975

Allen, Hugh D.
Tucson, Ariz.

Atwood, Gerald F.
Nashville, Tenn.

Berman, Michael Allen
Woodbridge, Conn.

Cohn, Herbert E.
Marblehead, Mass.

Eshaghpour, Eshagh
Berwyn, Pa.

Fish, Bernard G.
Bronx, N. Y.

Freed, Michael D.
Boston, Mass.

Galioto, Frank M., Jr.
West Simsbury, Conn.

Garcia, Otto L.
Miami, Fla.

Gathman, Gary E.
San Jose, Calif.

Gaum, Winston E.
Nova Scotia, Canada

Gillette, Paul C.
Houston, Texas

Gingell, Robert L.
Amherst, N. Y.

Hagler, Donald J.
Rochester, Minn.

King, Terry D.
River Ridge, La.

Kirkpatrick, Stanley E.
San Diego, Calif.

Laird, W. Pennock
Dallas, Texas

Levin, Daniel L.
Dallas, Texas

Nihill, Michael R.
Houston, Texas

Okoroma, Edwin O.
Nigeria

Park, Myung K.
Overland Park, Kansas

Sacks, Edmond J.
San Antonio, Texas

Sahn, David J.
Tucson, Arizona

Shapiro, Stephen R.
Washington, DC

Silverman, Norman H.
San Francisco, Calif.

Truccone, Nestor J.
Bloomfield Hills, Mich.

Vedam, Venkata Subrahmanyam
Forest Park, Ill.

Weinberg, Paul Morris
Levittown, Pa.

Young, Guillermo A.
West Los Angeles, Calif.

July 1975

Henken, Dale P.
Portland, Ore.

Karsh, Richard B.
Knoxville, Tenn.

Lewis, Alan B.
Los Angeles, Calif.

Rosengart, Ronald M.
Los Angeles, Calif.

Singh, Amarjit
New York, N. Y.

July 1974

Krongrad, Ehud
Harrington Park, N. J.

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

1975

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

1976

JAN. 11–13 — **Future Directions in the Management of Cardiac Disease: A Bicentennial Viewpoint.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC and James S. Forrester, co-directors. Snowmass-at-Aspen, Aspen, Colo.

JAN. 19–22 — **Core Curriculum: Pediatric Echocardiography.** Richard A. Meyer, director and Samuel Kaplan, FACC, co-director. Children's Hospital, Cincinnati, Ohio

FEB. 23–26 — **Twenty-fifth Annual Scientific Session.** Charles Fisch, FACC, president. Marriott Motor Hotel, New Orleans, La.

MAR. 11–13 — **Cardiovascular Disease—1976: Practical Diagnosis and Management.** John Ross, Jr., FACC, Robert A. O'Rourke, FACC, Joel S. Karliner, FACC and Kirk L. Peterson, FACC, directors. La Costa Resort Hotel and Spa, San Diego, Calif.

MAR. 22–26 — **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, Ind.

MAR. 26–27 — **New Perspectives in Exercise Stress Testing.** Myrvin H. Ellestad, FACC and William H. Allen, FACC, directors. Center for Health Education, Memorial Hospital of Long Beach, Long Beach, Calif.

APR. 5–14 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 7–9 — **Cardiovascular Disease 1976: Nuclear Medicine Approaches.** Lawrence S. Cohen, FACC, director and Gerald Freedman, Alexander Gottschalk and Barry L. Zaret, FACC, co-directors. Yale University School of Medicine, New Haven, Conn.

APR. 24–27 — **A Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC, director and Leo Schamroth, FACC, co-director. Sheraton Sand Key Hotel, Clearwater, Fla.

APR. 26–29 — **Current Concepts in Cardiology—1976.** Philip R. Akre, director and Masato Takahashi, FACC and John A. Bowers, co-directors. Caesars Palace, Las Vegas, Nev.

APR. 26–30 — **Consultant's Course in Cardiology.** Simon Dack, FACC, and Michael V. Herman, FACC, directors. Mount Sinai Medical Center, New York, N.Y.

APR. 28–30 — **Basic Vectorcardiography.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

MAY 6–8 — **Arrhythmias: Basic and Clinical Considerations.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. Holiday Inn, San Francisco, Calif.

MAY 10–13 — **Frontiers in Cardiology.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Royal Coach Motor Hotel, Atlanta, Ga.

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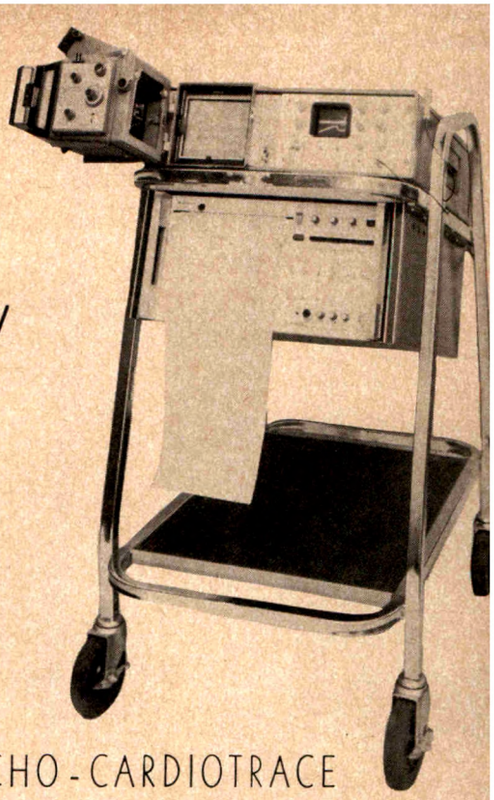

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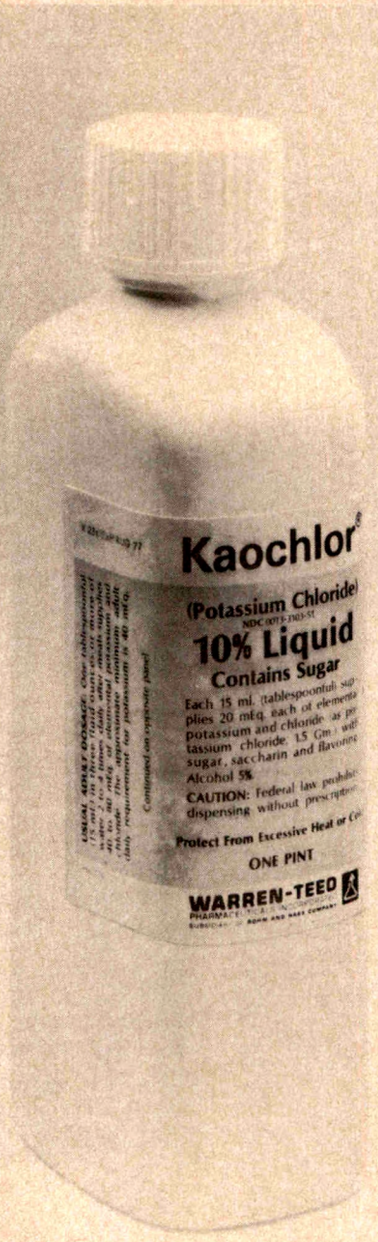

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Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later. Tablets should not be chewed.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also in unit dose—package of 10 x 10 strips (N 0047-0004-11).

Additional Dosage Forms: Peritrate 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also in unit dose—package of 10 x 10 strips (N 0047-0001-11). Peritrate 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

Full information is available on request.

Defense against attack.

For over 22 years, Peritrate® has been considered by many physicians as one of the top defensive measures for patients with angina pectoris. In many patients Peritrate used prophylactically helps decrease the frequency and severity of angina attacks.* With minimal side effects.

Peritrate can also help reduce nitroglycerin requirements and, therefore, nitroglycerin side effects. Is it any wonder so many physicians continue to prefer Peritrate prophylaxis for their angina patients?

LONG-ACTING PROTECTION AGAINST ANGINA PAIN*

Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) 80mg

Warner/Chilcott
Div. Warner-Lambert Company
Morris Plains, N.J. 07950
PE-GP-51

The Great Wall of China, an immense 1,400-mile-long man made barrier 20 to 30 feet high and 15 to 20 feet thick, helped defend China from the attack of Mongol hordes for more than 2,000 years.

*The drug has been evaluated as possibly effective for this indication.
See brief summary.

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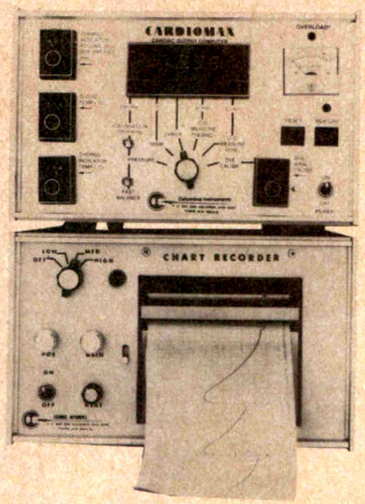

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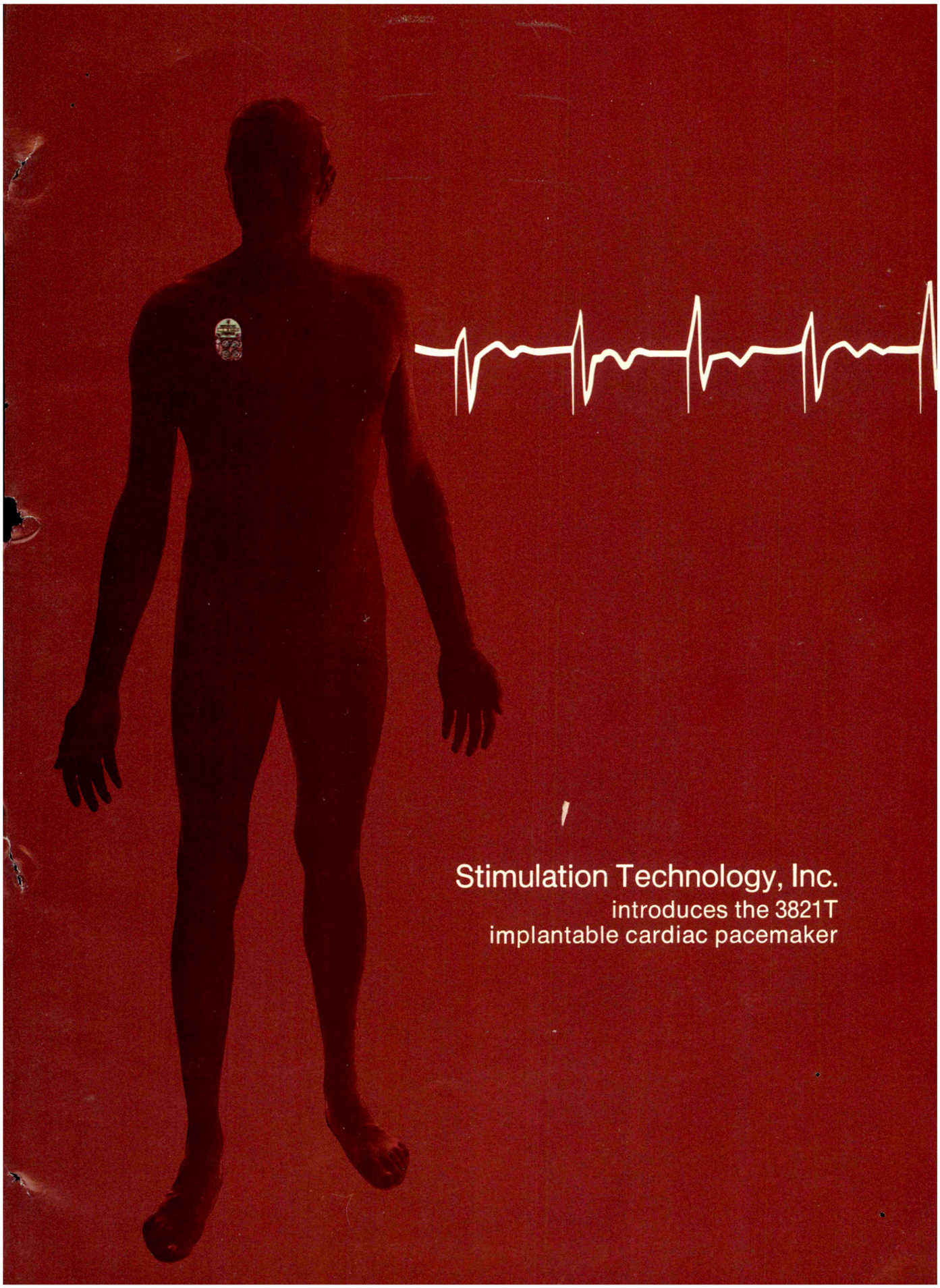

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introduces the 3821T
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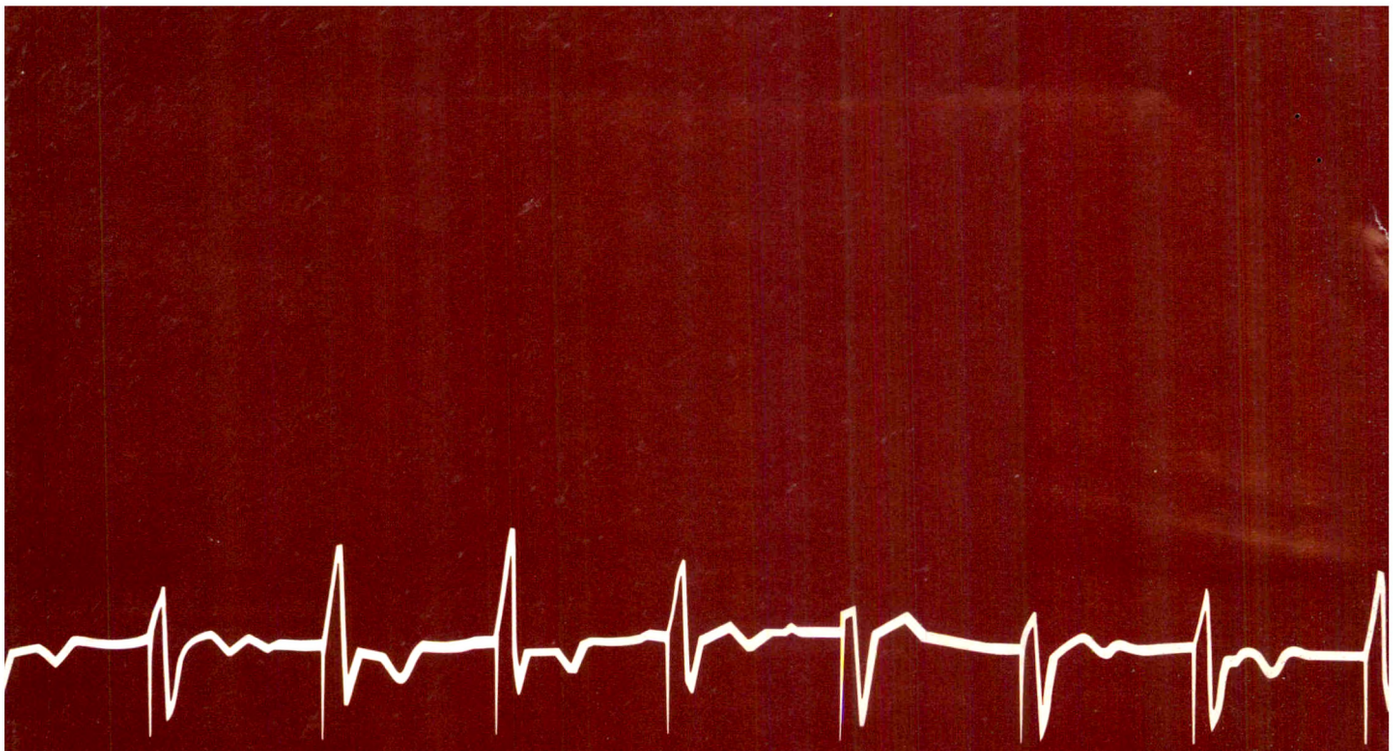

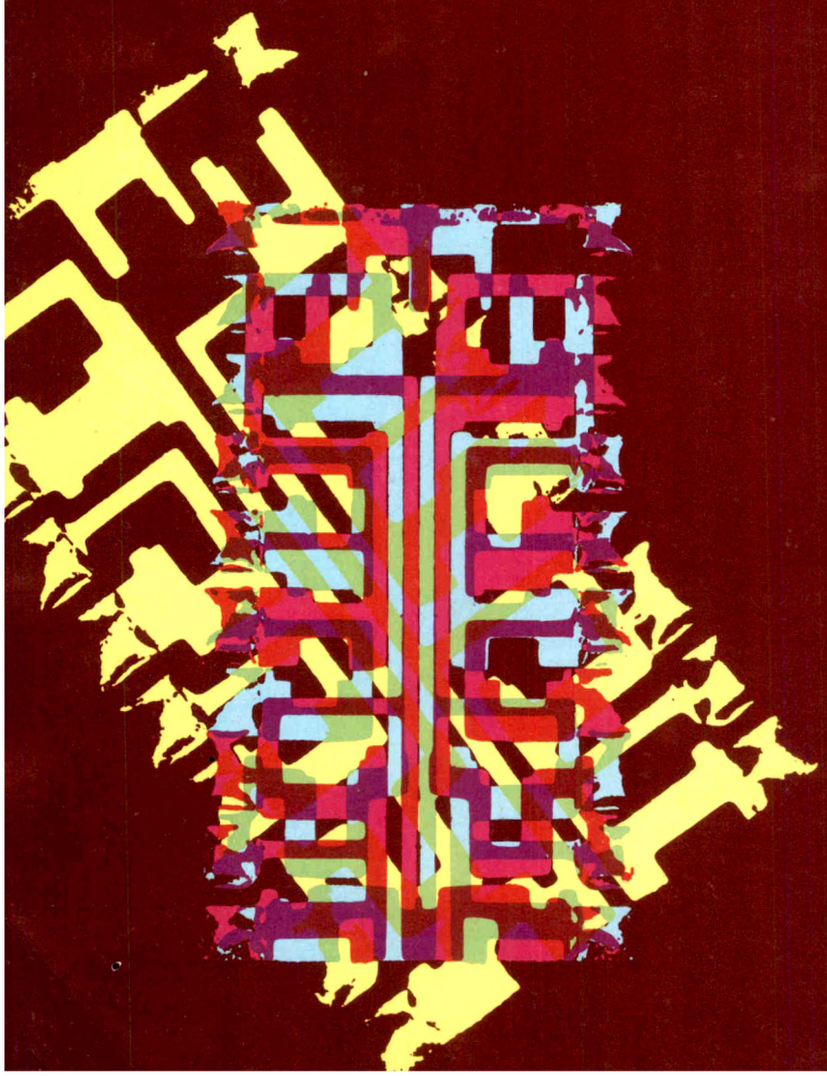

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The 3821T demand pacemaker

Actual Size

specifications:

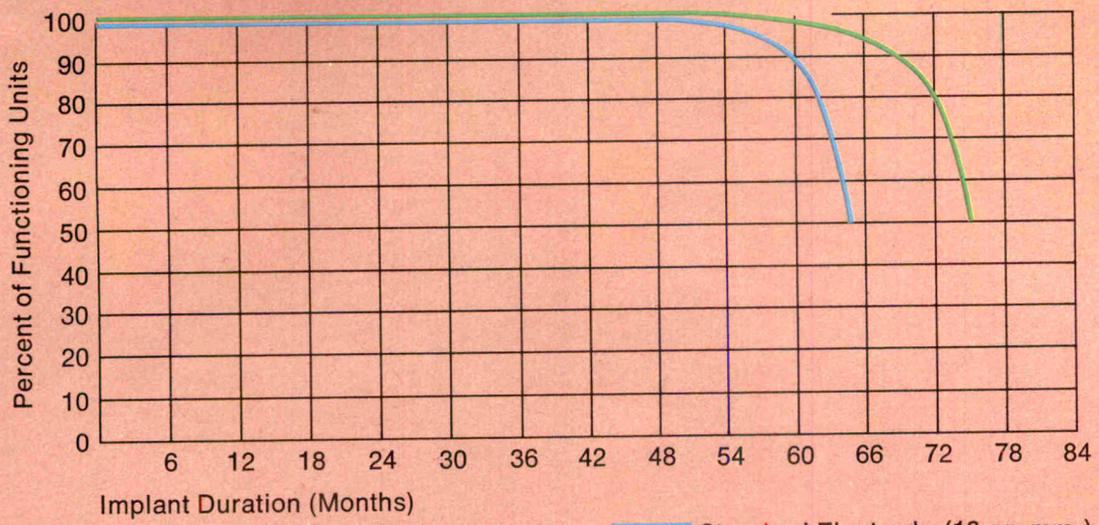
length	7.3 cm
width	4.7 cm
thickness	2.3 cm
weight	130 gm
basic rate	71 ± 4 ppm
hysteresis rate	60 ppm nominal
interference rate	105 ppm nominal
reed switch operated rate	105 ppm nominal

(Rates given apply to implanted (37° C) operation at normal battery voltage; exact rates, at room temperature, are shown on registration and information form enclosed with each pulse generator.)

features of the 3821T

- unipolar
- hybrid micro circuit construction
- battery depletion warning circuit
- unique interference handling capability
- hermetically sealed electronics
- small size
- lightweight

Pacemaker Battery -- Projected Longevity *



* These longevity projections are based on theoretical calculations for the pulse generator battery life only and do not account for pacemaker malfunction due to random component failure or events which have no relationship to time. The results therefore may not represent actual pacemaker longevity. The above projections are made on the basis of chemical capacities, self-discharge rates, and current drains measured using standard and micro electrodes, and no inhibition. Calculations include empirical data and extrapolations based upon actual battery life experience, projections from improvements in the new double separator cell and effects of one year pulse generator storage prior to implant.

Caution: U.S. federal law restricts this device to sale by or on the order of a physician.

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The patient with cardiac arrhythmia may need medication most when he's least likely to take it...

while he's sleeping.

Quinaglute® Dura-Tabs® (quinidine gluconate)

- produces sustained serum quinidine levels, thus providing a convenient 8 or 12 hour dosage schedule
- usually insures uninterrupted therapeutic quinidine gluconate levels during sleep
- avoids peaks and valleys in plasma levels during which time the arrhythmias may recur
- maintains normal sinus rhythm following conversion by other techniques
- well tolerated to enhance patient cooperation — few G.I. disturbances

Contraindications: Quinaglute Dura-Tabs are contraindicated in patients with partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening; in patients manifesting idiosyncrasy or sensitivity to quinidine (e.g. febrile reactions, skin eruptions, thrombocytopenia, etc.), in patients with renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. It may be contraindicated in certain patients who have marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered; especially during the first weeks of therapy.

Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm.

As with other quinidine products, Quinaglute Dura-Tabs should not be used during pregnancy.

Adverse Reactions: The patient should be advised to report immediately to the physician any symptoms of cinchonism (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis and respiratory distress).

Where such symptoms develop, or if evidence of hypotension appears, the drug should be discontinued. Gastrointestinal disturbances have only rarely been reported. If they occur, they may be minimized by administering the drug with food. If they persist, dosage should be decreased.

Dosage: For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours.

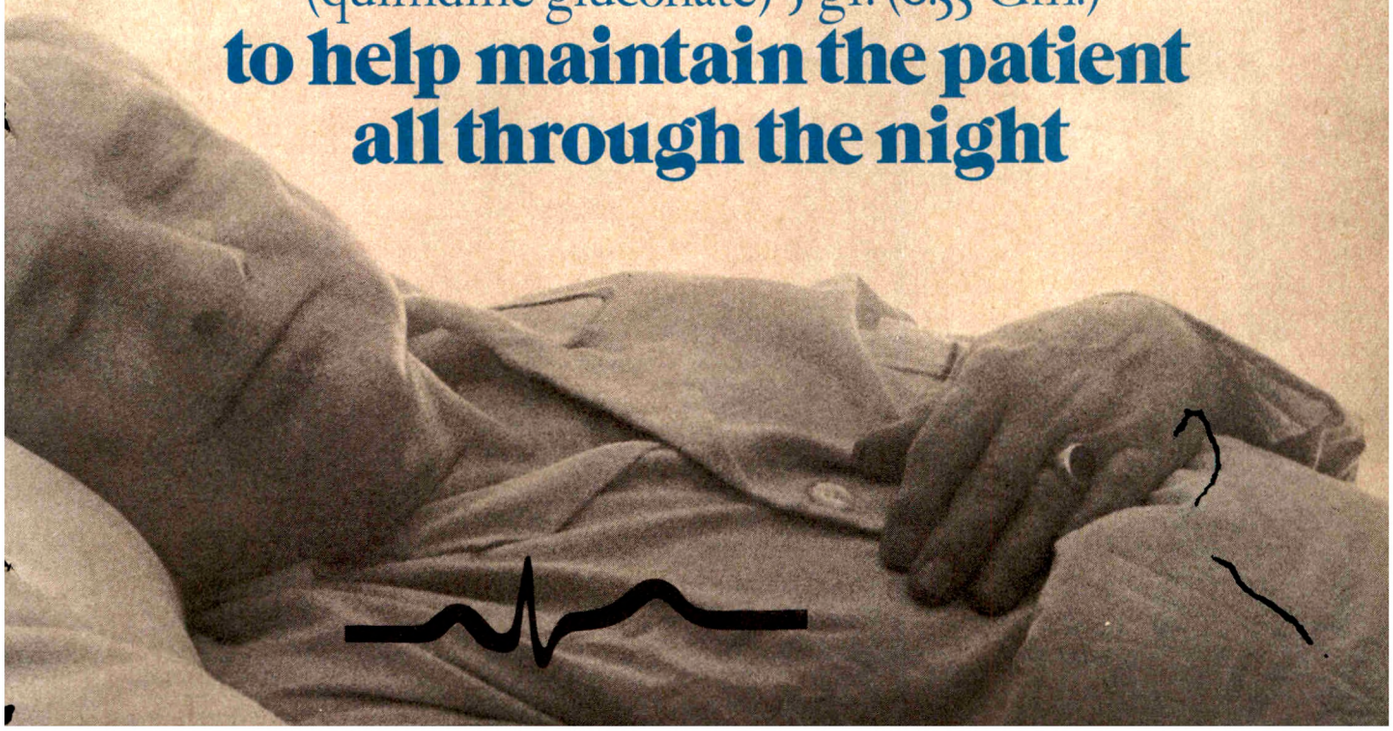
Before prescribing or administering, please refer to QUINAGLUTE full product information.

Cooper Laboratories, Inc.
Wayne, New Jersey 07470

Quinaglute® Dura-Tabs®

(quinidine gluconate) 5 gr. (0.33 Gm.)

to help maintain the patient all through the night



Principles of oral anticoagulation

Practical Considerations

Identifying your patient at risk of thromboembolic complications

While every MI patient is not a candidate for oral anticoagulation therapy, a history of previous infarct or angina, persistent atrial fibrillation or congestive failure, severe hypotension or shock or serious arrhythmia may increase risk of thromboembolic complications.

In addition, certain procedures often place your surgical patient, particularly if he's over 40 years of age, in the high risk category—cup arthroplasty or pelvic surgery, heart valve replacement, reparative vascular surgery.

Your geriatric patient, too, is at high risk of thromboembolism if he's suffered a fracture—especially of the hip, pelvis or a lower extremity—or if his history includes venous insufficiency.

For any of these individuals, obesity, previous episodes of venous thrombosis or pulmonary embolism and a future including prolonged bed rest all increase the risk of thromboembolic complications, and make him a candidate for oral anticoagulation.

Laboratory monitoring

For every patient receiving COUMADIN® (*crystalline* sodium warfarin), frequent laboratory monitoring is a key to effective therapy. Determine prothrombin time daily until results stabilize in the therapeutic range —1½ to 2½ times normal. Individualize dosage and administration as indicated by prothrombin time results. Determine subsequent prothrombin times periodically throughout the course of therapy.

Educating your patient

Because a patient is generally more reliable if he understands his condition and his medication, he should be made aware of the factors that may influence his prothrombin time and, therefore, his response to COUMADIN®—dietary change, travel, other medication, change in physical condition and abrupt environmental change. What's more, he should know the importance of regularly taking the exact dosage of COUMADIN® prescribed and of keeping every appointment with you and with the laboratory.

COUMADIN® is an Endo U.S. registered trademark.

Therapeutic principles put into practice

COUMADIN®
(CRYSTALLINE SODIUM WARFARIN*)

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional and lumbar block anesthesia.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Pregnancy–COUMADIN® passes through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage **in utero,** even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. The newborn may be particularly sensitive to sodium warfarin. There have been reports of birth malformations in children born to mothers who have been treated with warfarin during the first trimester of pregnancy. Whether warfarin was in fact the responsible agent has not been established. Therefore, women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed. If COUMADIN® must be used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks. **Lactation**–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Spinal puncture. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN®.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methylphenidate; monoamine oxidase inhibitors; nalidixic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates (in excess of 1 Gm/day); sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K-dependent factors, namely Factors VII, IX, X and II, the factors affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN® may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time; and therefore, when patients are receiving both heparin and COUMADIN®, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN® may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Water for Injection. 75 mg: Unit consists of 1 vial, 75 mg; sodium chloride, 15 mg; thimerosal, 0.3 mg. pH is adjusted with sodium hydroxide, accompanied by a 3 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

Rev. April, 197

*Present as crystalline sodium warfarin isopropanol clathrate.

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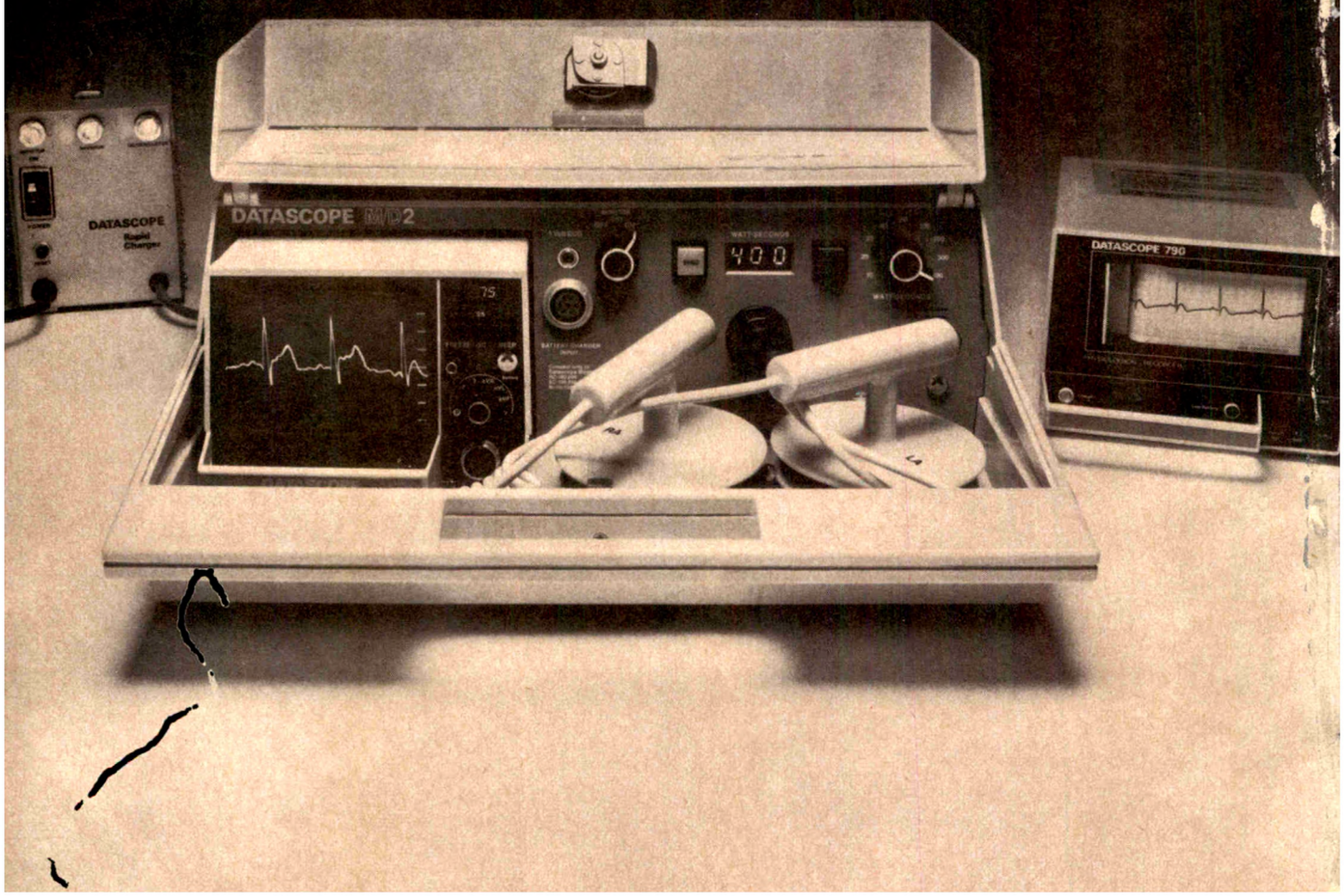
THE DATASCOPE M/D2 SYSTEM. THE FIRST RESCUE SYSTEM AS FLEXIBLE AS THE PEOPLE WHO USE IT.



If there's one thing you can be sure of in cardiac rescue, it's that you can't be sure of anything.

Every situation, either in the hospital or in the field, presents new problems, and requires new solutions.

At Datascope, we've been in emergency medicine since its inception.

Our equipment has faced just about everything. And from that experience we've put together a system that's prepared to face anything: the M/D2 System.

The M/D2 System is built on one very simple principle. *Every instrument in the system must be independent and not compromised by any other instrument.*

In keeping with this philosophy, our monitor, our defibrillator and our strip-chart recorder each have a separate battery source. One unit never puts a drain on another.

But to see its flexibility, let's take our system apart, instrument by instrument.

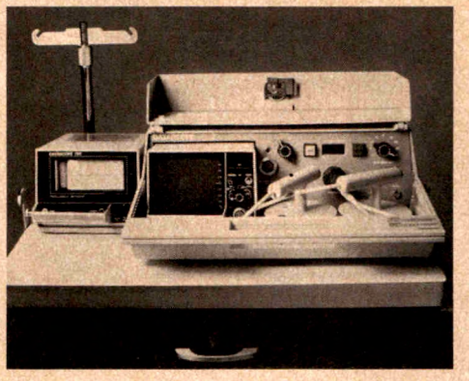
OUR MONITOR.

The monitor in the M/D2 System nests inside the defibrillator. You can carry the monitor and defibrillator, use it, and store it as one unit.

But the monitor pulls out* of the M/D2 case and works as a separate unit as well. So it can be placed right on a patient's stretcher in the field. Or put in the most advantageous viewing position at the bedside.

In addition to being so flexible, our monitor outperforms any monitor in emergency medicine.

It has a 5-inch scope with a 8 x 11 cm. viewing area.



It has a memory which provides a bright, non-fade display that's remarkably clear even in strong sunlight.

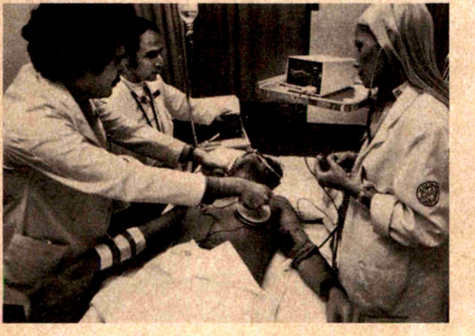
It has a freeze button which lets you stop the ECG for closer study.

It's the only emergency monitor with a digital heart rate readout. And because the readout is an LED display, you can even read it in the dark.

OUR DEFIBRILLATOR.

Like our monitor, our defibrillator has its own battery-pack.

It's the only defibrillator made that gives you a *digital* energy meter. Which displays both stored energy and the results of delivered energy tests.



The defibrillator is exceptionally safe. A warning tone sounds when the selected energy level is reached.

Energy cannot be delivered unless the push-button switch on each paddle is actuated simultaneously.

The energy within the defibrillator is automatically discharged when the unit is turned off.

For paramedic use, the M/D is available completely shielded against RF interference across the entire communications band

OUR RECORDER.

Our recorder is flexible as well. It's carried separately and powered separately. (For good reason. A recorder powered by common battery puts an enormo drain on the other instruments i the system.)

Our recorder weights only pounds. And when you're using our monitor outside the M/D2 case, our recorder fits right into the space the monitor vacated. Which allows even easier transpo

OUR RAPID CHARGER.

Although the M/D2 comes with a standard battery recharg we offer the first rapid rechargi unit as part of our system. Our Rapid Charger allows you to de fibrillate with just 60 seconds of recharge. And in just 10 minutes it will recharge the defibrillator at least 60% of total capacity.

THE SYSTEM. IT'S MORE THAN ANY OF ITS PARTS

Three independent units. Three independent battery-pac And a Rapid Charger. They wor together, or apart. They give yo more ability to react than any single unit ever could.

For more information on th M/D2 System, write: Datascope Corp., 580 Winters Avenue, Paramus, N.J. 07652.

THE DATASCOP M/D2

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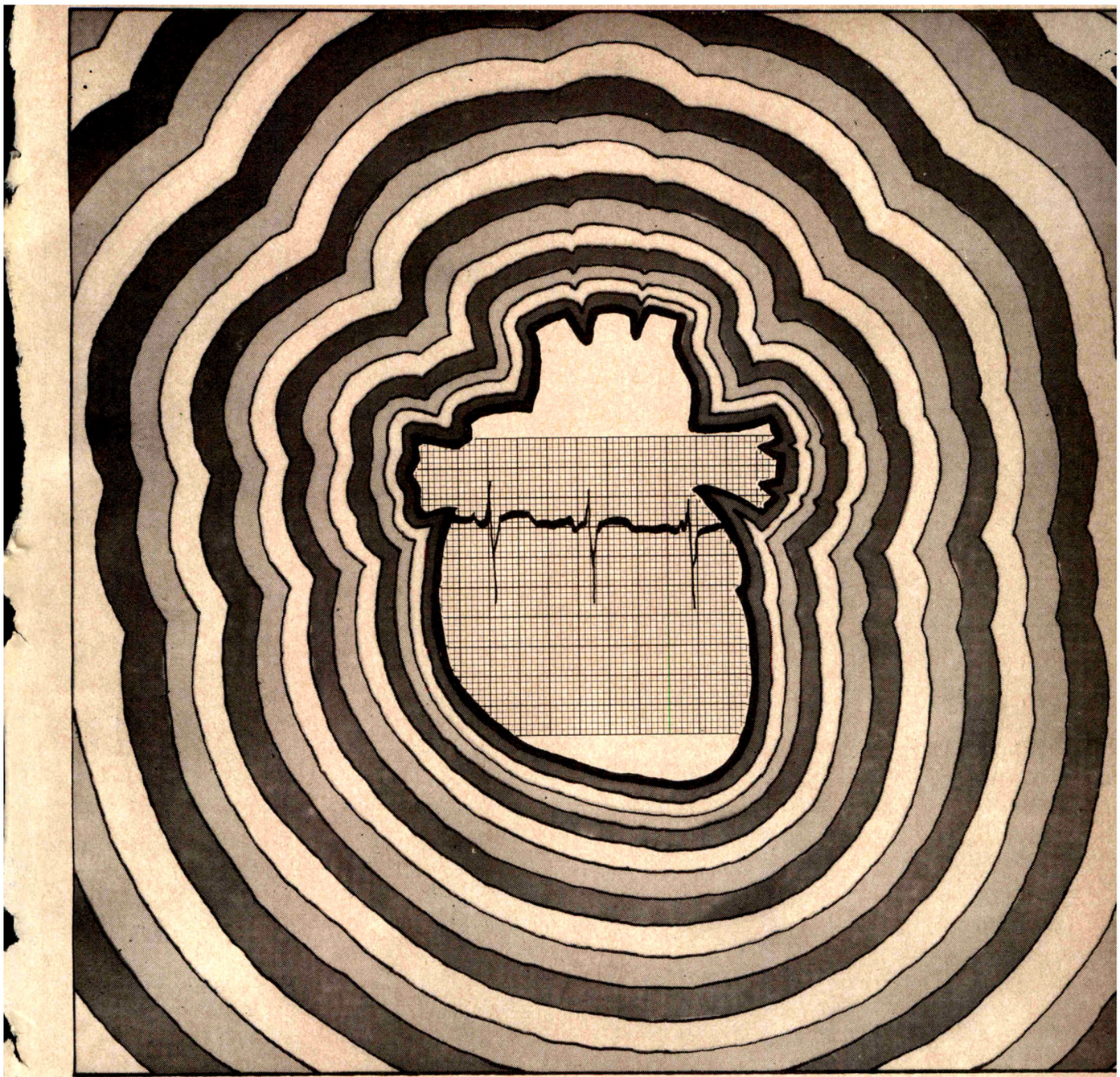

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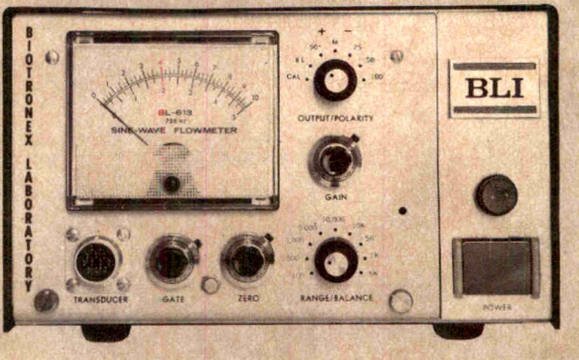

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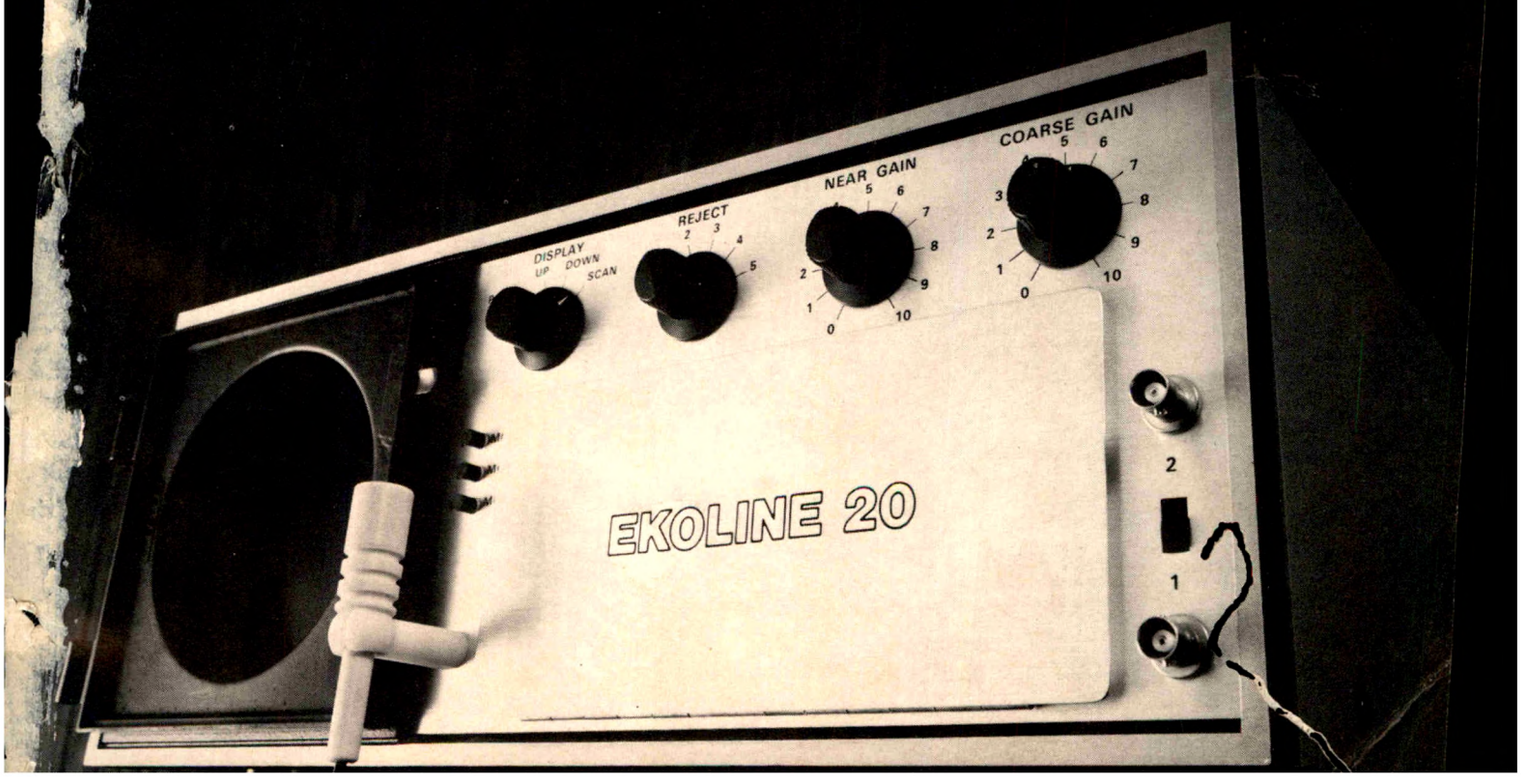

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